Clinical Study Protocol

A MULTICENTER, CLUSTER RANDOMIZED SUPERIORITY TRIAL OF A GUIDELINE-BASED FAMILY SUPPORT INTERVENTION IN INTENSIVE CARE UNITS

(FICUS Trial)

Study Type:	Health-related intervention
Study Categorization:	Other Clinical Trial Category A
Study Registration:	Intended registry: ClinicalTrials.Gov
Study Identifier:	SNCTP000004842, NCT05280691
Sponsor:	Prof. Dr. phil. Rahel Naef, RN
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Study Intervention:	Guideline-based, nurse-led, interprofessional family support intervention in intensive care
Protocol Version and Date:	Version 1.1, 21.06.2022

SIGNATURE PAGES

Study number	SNCTP000004842, NCT05280691
Study Title	A MULTICENTER, CLUSTER RANDOMIZED SUPERIORITY TRIAL OF A GUIDELINE-BASED FAMILY SUPPORT INTERVENTION IN INTENSIVE CARE UNITS (FICUS Trial)

Sponsor & Coordinating Investigator

This clinical trial protocol was subject to critical review and has been approved by the Sponsor-Coordinating Investigator and Co-Coordinating Investigators. The information herein is consistent with

- the current risk/benefit evaluation of the intervention
- the moral, ethical, and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, Good Clinical Practice.

Prof. Dr. phil. Rahel Naef, RN

Zürich, 21.06.2022 — Place/Date

R Naef — Signature

Co-Coordinating Investigators

Prof. Dr. med. Miodrag Filipovic

St. Gallen, 13.06.2022 — Place/Date

Signature

Dr. phil. Marie-Madlen Jeitziner, RN

Bern, 10.06.2022 — Place/Date

Marie-Madlen Jeitziner — Signature

Biometrician

Dr. Stefanie von Felten

Zürich, 21.6.2022 — Place/Date

Stefanie von Felten — Signature

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I have read and understood this protocol and agree to conduct the trial as set out in this study protocol.

Site	University Hospital Zurich Institute of Intensive Medicine Trauma Intensive Care Unit Rämistrasse 100 CH-8091 Zürich
Principal investigator	KD Dr. med. Peter Steiger

Zürich, 21/06/22 _____

Place/Date Signature

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Site	University Hospital Zurich Institute of Intensive Medicine Cardiac Intensive Care Unit Rämistrasse 100 CH-8091 Zürich
Principal investigator	Paola Massarotto, MScN, RN

Zürich, 28.6.2022
Place/Date

P. Massarotto
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Principal investigator	Dr. med. Benjamin Hertler

Zürich, 17.06.2022 _____

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Local Principal Investigator at study site:

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Site	Cantonal Hospital of St. Gallen Clinic of Intensive Medicine Rorschacher-Strasse 95 CH-9007 St. Gallen
Principal investigator	Ursula Betschart, RN

St. Gallen 16. Juni 22 _____

Place/Date Signature

Local Principal Investigator at study site:

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St. Gallen 16.6.2022 _____

Place/Date

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Signature

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Site	Inselspital, University Hospital Bern Department of Intensive Care Medicine Murtenstrasse 10 CH-3010 Bern
Principal investigator	Dr. med. Björn Zante

Bern 28/6/22

Place/Date

Signature

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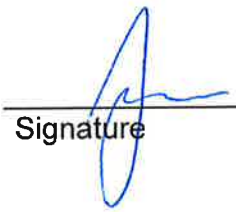
Principal investigator	Dr. med. Jan Wiegand

Bern, 15.6.2022
Place/Date



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Site	Graubünden Cantonal Hospital Loëstrasse 170 CH-7000 Chur
Principal investigator	Dr. sc. med. Hanna Burkhalter, RN

Chur 15. Juni 2022
Place/Date

Signature

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Site	Lucerne Cantonal Hospital Centre of Intensive Care Medicine Spitalstrasse CH-6000 Luzern 16
Principal investigator	Fabienne Lussmann, BScN, RN

Luzern, 16.06.22 F. Lussmann

Place/Date Signature

Local Principal Investigator at study site:

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Site	Spital Thurgau AG Cantonal Hospital Frauenfeld Interdisciplinary Intensive Care Unit Postfach CH-8501 Frauenfeld
Principal investigator	Prof. Dr. med. Alexander Dullenkopf

F' feld, 16.6.22 _____
Place/Date

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Local Principal Investigator at study site:

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Site	Solothurn Hospitals Cantonal Hospital Olten Baslerstrasse 150 CH-4600 Olten
Principal investigator	Dr. Christoph von Dach, RN

15.6.22

Place/Date

Signature

Local Principal Investigator at study site:

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Site	Hospital Thun Interdisciplinary Intensive Care Unit Krankenhausstrasse 12 CH-3600 Thun
Principal investigator	Dr. med. Antje Heise

Thun 17.6.22 — Place/Date

A. Heise — Signature

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Site	Institute for Anesthesiology and Intensive Medicine Hirslanden AG, Klinik Hirslanden Zürich Witellikerstrasse 40 8032 Zürich
Principal investigator	Monique Wenzler, RN

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Place/Date

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Local Principal Investigator at study site:

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Site	Interdisciplinary Intensive Medicine Cantonal Hospital Baden AG Im Ergel 1 5404 Baden
Principal investigator	Yvonne Liebert, MScN, RN

Baden, 20.06.22
Place/Date

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Site	Zentrum für Intensivmedizin Kantonsspital Winterthur Brauerstrasse 15, Postfach 8401 Winterthur
Principal investigator	Dr. med. Karl Philipp Bühler

Winterthur 15.06.22

Place/Date Signature

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AE	Adverse Event
AG	Canton of Aargau
AI	Canton of Appenzell Innerrhoden
AIS	Abbreviated Injury Scale
ALCOA+	Attributable, Legible, Contemporaneous, Original, and Accurate + Complete, Consistent, Enduring, and Available
AR	Canton of Appenzell Ausserrhoden
Art.	Article
ASR	Annual Safety Report
AUC	Area Under the Curve
BAIA	Arconym for "Beziehungsaufbau, Assessment, Intervention, Abschluss"
BE	Canton of Bern
BL	Canton of Basel-Landschaft
BRS-6	Brief Resilience Scale
BS	Canton of Basel-Stadt
CEC	Competent Ethics Committee
CISCO	Chief Information Security Officer
ClinGov	Clinical Governance Services
ClinO	Clinical Trial Ordinance (KlinV)
COVID-19	Coronavirus Disease 2019 (SARS-CoV-2 virus)
CRA	Clinical Research Associate
CRF	Case Report Form
CTC	Clinical Trial Center
CTU	Clinical Trials Center at the University Hospital Zurich / University of Zurich
d	Days
DPA	Swiss Federal Act on Data Protection
DPO	Ordinance to the Swiss Federal Act on Data Protection
DT	Distress Thermometer
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eFMRO	Electronic Family-Reported Outcome
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
EKOS	Ethikkommission Ostschweiz
EOS	End of Study
EOT	End of Treatment
EU	European Union
EuroQol	European Quality of Life Scale
FAD-GF-12	Family Assessment Device General Functioning Scale
FAIR	Findability, Accessibility, Interoperability, and Reusability
FDA	US Food and Drug Administration
FFC	Family-Centered Care
FICUS	Family Support Intervention in Intensive Care Units
FPI	First Participant In

FR	Canton of Freiburg
FSI	Family Support Intervention
FS-ICU-24R	Family Satisfaction with ICU Care Questionnaire
FUx	Follow-Up Timepoint
GCP	Good Clinical Practice
GL	Canton of Glarus
GR	Canton of Graubünden
h	Hours
HADS-14	Hospital Anxiety and Depression Scale
MDSi	Minimaler Datensatz der SGI
HIPAA	Health Insurance Portability and Accountability Act
Hx	Hypothesis Number
ICC	Intra-Cluster Correlation Coefficient
ICE-FPSQ-14	Family Perceived Support Questionnaire
ICH	International Council on Harmonization
ICT	Central Information Technology Services, University of Zurich
ICU	Intensive Care Unit
IES-6	Impact of Events Scale-6
IMC	Intermediate Care
IP	Intellectual Property
JU	Canton of Jura
Katz ADL	Katz Index of Independence in Activities of Daily Living
KlinV	Verordnung über klinische Versuche
Lawton IADL	Lawton Instrumental Activities of Daily Living Scale
LPI	Last Participant In
LU	Canton of Luzern
MDSi	Minimal Data Set (as provided by the Swiss Society of Intensive Medicine)
mo	Months
MRC	Medical Research Council
MySQL	Database Software Name (Structured Query Language)
NA	Not Available
NCCR	US National Center for Research Resources
ND	Not Done
NEMS	Nine Equivalents of Nursing Manpower Use Score
NIH	US National Institute of Health
NW	Canton of Nidwalden
ODPC	Ordinance on Data Protection Certification
OW	Canton of Obwalden
pCRF	Paper Case Report Form
PFAG	Patient and Family Advisory Group
PHP	Programming Language PHP (Hypertext Preprocessor)
PI	Principal Investigator
PICS-F	Post-Intensive Care Syndrome – Family
QQPPI-14	Questionnaire on Quality of Physician-Patient Interaction
QR	Quick Response

R	Programming Language R
Rand	Randomization
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAPS-2	Simplified Acute Physiology Score II
SG	Canton of St. Gallen
SGI	Swiss Society of Intensive Medicine
SH	Canton of Schaffhausen
SMS	Short Message Service
SMTP	Simple Mail Transfer Protocol
SNCTP	Swiss National Clinical Trials Portal
SNSF	Swiss National Science Foundation
SO	Canton of Solothurn
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SWLS-5	Satisfaction with Life Scale
SZ	Canton of Schwyz
TG	Canton of Thurgau
Tx	Assessment Timepoint
UK	United Kingdom
UR	Canton of Uri
US	United States of America
VALUE	Mnemonic Value, Acknowledge, Listen, Understand, Encourage
VAS	Visual Analog Scale
VS	Canton of Wallis
WHO	World Health Organization
WHO-5	WHO-5 Well-Being Index
wks	Weeks
WR	Working Instruction
Y	Discharge from ICU
ZG	Canton of Zug
ZH	Canton of Zürich

STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dr. phil. Rahel Naef, RN Institute for Implementation Science in Health Care, Faculty of Medicine, University of Zurich Center of Clinical Nursing Science, University Hospital Zurich
Study Title:	A MULTICENTER, CLUSTER RANDOMIZED SUPERIORITY TRIAL OF A GUIDELINE-BASED FAMILY SUPPORT INTERVENTION IN INTENSIVE CARE UNITS
Short Title / Study ID:	FICUS Trial
Protocol Version and Date:	Version 1.1, 21.06.2022
Trial registration:	SNCTP000004842, NCT05280691
Study category	Other clinical study category A
Background:	Family members are important to the well-being and recovery of critically ill persons yet are themselves profoundly affected by the critical illness. During a close other's treatment in an intensive care unit (ICU), families experience high levels of stress and uncertainty, particularly in the event of surrogate decision-making and loss. Poor communication, insufficient shared decision-making, and inadequate emotional and practical support by intensive care staff have been found to add to families' burden. Poor quality of care has been associated with adverse mental health outcomes, which is reported by 20-60% of family members. A lack of engagement and support, coupled with acute stress, not only increases family suffering, but affects family members' functioning in everyday life, and limits their ability to engage in caregiving activities needed by the survivor of critical illness or cope with their loss.
Rationale:	To increase the quality of family care and prevent adverse mental health outcomes, ICU guidelines recommend family engagement, communication, and support as well as the use of specific roles, but the evidence base for these recommendations is weak to date. Only a few studies have investigated family support interventions that consist of structured communication and / or specific family nursing roles. Promising effects have been found on family members' communication and support experience. However, findings on psychological distress remain inconclusive whereas insight on family management ability is virtually absent. Moreover, best practice around family engagement in ICU is often not implemented consistently in routine care. Hence, real-world evidence generated by randomized controlled designs is necessary to establish the effect of such multi-component interventions on quality of family care and their potential in supporting family management of critical illness and in reducing adverse mental health outcomes.

Objective(s):	The study aims to determine the effect of a nurse-led, interprofessional family support intervention on quality of family care, family management, and individual mental health compared to usual care provided to family members. The study also aims to explore implementation barriers / facilitators and to examine if the implementation strategy shows sufficient promise for scale up.
Outcome(s):	The primary study endpoint is quality of family care, operationalized as family members' satisfaction with ICU care at discharge. Secondary endpoints include quality of communication and nurse support, family management of critical illness (functioning, resilience) and family members' mental health (well-being, psychological distress) measured at admission, discharge, and after 3, 6, and 12 months.
Study design:	The trial is designed as a multi-center, parallel-cluster randomized, superiority trial with 16 clusters of ICUs in the German-speaking part of Switzerland.
Inclusion / Exclusion criteria:	Potential participants are family members of critically ill persons admitted to a study ICU. A family member is defined as a close other from the patient's perspective, as noted in the clinical record or in advanced directives, or as indicated by the legally defined surrogate decision-maker. Inclusion criteria regarding patients: • Expected length of stay in ICU ≥48 hours, as predicted by the intaking ICU clinician (physician or nurse) at admission AND • Life-threatening condition with a high risk of death or long-lasting functional impairment OR high risk of prolonged mechanical ventilation (>24 hours). Inclusion criteria regarding family members (all must apply): • Primary support person of the patient. • Able to complete family-reported outcome measures (questionnaires) in German language. • Age ≥18 years. • Signed informed consent form. Exclusion criteria regarding patients (one leads to exclusion): • Preexisting declined general consent. • ICU stay <48 hours. Exclusion criteria regarding family members (one leads to exclusion): • Prior inclusion in FICUS trial on another study ICU. • Cognitive inability to understand the study or complete the questionnaire as appraised by clinicians and / or study recruitment staff. • Inability to complete baseline data collection within the required timeframe after admission / study enrollment (Calvert et al., 2018).

Study Intervention:	In addition to usual care, families in the intervention group will receive (1) specialist nurse support along the patient pathway at defined time-points, from admission to discharge including follow-up care, and (2) nurse-coordinated liaison and structured, interprofessional communication by the ICU team. The intervention is grounded in a family systems approach and guideline-based strategies for family engagement in the ICU and has been pilot-tested in one ICU.
Reference Intervention:	Family members in the control group will receive usual care.
Number of Participants with Rationale:	The projected sample size is 896 family members of critically ill patients treated in acute care hospitals in the German-speaking part of Switzerland. To account for a drop-out rate of 10% of participants within clusters (without drop-out of whole clusters), an average number of 56 participants should be recruited per cluster, resulting in a total of 896 family members over all 16 clusters.
Study Duration:	The duration of the main study phase is 30 months from the recruitment of the first participant to the last follow-up measurement of the last participant. This main phase is preceded by a preparatory phase and followed by an analysis phase, each lasting 6 months, which corresponds to a total study duration of 42 months. From the individual participant's perspective, the study initiates after recruitment, which takes place within four days after the patient's admission to ICU, and concludes with the last follow-up assessment 12 months after discharge of the patient from ICU (+/-14 days), amounting to a total duration of 12 months plus the duration of the patient stay in ICU.
Study Schedule:	Month Year of First-Participant-In (planned): 04/2022 Month Year of Last-Participant-Out (planned): 09/2024
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Study Center(s):	This multi-center trial is designed to involve 16 ICUs (i.e. clusters), treated as separate study centers, located in the following hospitals: - University Hospital Zürich, Institute of Intensive Medicine (4 clusters) - Cantonal Hospital of St. Gallen (2 clusters) - University Hospital Bern, Department of Intensive Care Medicine - Lindenhof-Spital Bern, Intensive Care Unit - Graubünden Cantonal Hospital Chur, Intensive Care Unit - Lucerne Cantonal Hospital, Department of Intensive Care Medicine - Spital Thurgau AG, Cantonal Hospital Frauenfeld, Intensive Care Unit - Cantonal Hospital Olten, Solothurn Hospitals, Intensive Care Unit - Hospital Thun, Intensive Care Unit - Hirslanden Clinic Zurich, Intensive Care Unit - Cantonal Hospital Baden, Interdisiplinary Intensive Medicine - Cantonal Hospital Winterthur, Center for Intensive Medicine
Statistical Considerations:	The quantitative data will be analysed using linear mixed-effects models with a random intercept per cluster to estimate the effect of the study intervention. Satterthwaite approximation of the denominator degrees of freedom will adjust for the small number of clusters. Multiple imputation will be implemented to test the sensitivity of results to missing data. To account for a drop-out rate of 10% of participants within clusters (without drop-out of whole clusters), an average number of 56 participants should be recruited per cluster, resulting in a total of 896 family members over all 16 clusters.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

STUDY SCHEDULE

The study is scheduled to last 42 months, with a six-month preparatory phase, 18-month recruitment period, 12-month follow-up after enrollment of the last participant, and a six-month analysis and reporting phase. Table 1 shows the timeline of the cluster study processes, while Table 2 shows the timeline of the individual participant.

Table 1: Cluster timeline

Task / Timepoint	**Recruitment**	**Baseline Assessment**	**Randomization**	**First patient-In (FPI)**	**FU 1 - Intermediate assessment***	**FU 2 - Final assessment (EOT of Last Participant-In)****
Time frame / Timeline	Rand (-180d)	Rand (-30d)	Rand	FPI (R+180d)	FPI +12mo (+/-1mo)	FPI +18mo (+/-1mo)
Enrollment						
Recruitment of accredited ICUs as clusters	X					
Clusters informed about their assignment to intervention or control arm			X			
Implementation (intervention arm only)						
Implementation activity and cost log			X	X	X	X
Assessments (both study arms)						
ICU characteristics (SGI Minimal Data Set)		X			X	X
Quality of family care (Hwang et al., 2017)		X			X	X
Degree of family engagement (Institute for Healthcare Improvement, 2013)		X			X	X

FU = Follow-up, FPI = First Participant-In, EOT = End of Treatment, LPI = Last Participant-In, Rand= Randomization

*not applicable if FU 2 is before FPI +12 months, ** timeline projected based on the assumption that the duration from first participant-in to last-participant-in is 18 months.

Table 2: Individual participant timeline

Task / Timepoint	Admission to ICU	Screening	Informaiton	ICF	Baseline Assessment (T0)	FU 1 - Discharge from ICU (T1)	EOT & FU 2 - 3 months (T2)	FU 3 - 6 months (T3)	FU 4 - 12 months (T4) = EOS
Time frame / Timeline	0-24h	0-48h	0-72h	0-96h	0-96h	Y (-24h/ +14d)	Y+90d (+/14d)	Y+180d (+/-14d)	Y+365 (+/-14d)
Enrollment*									
Eligibility screen of patient**	X								
Identification of eligible family member**		X							
Information of family member** / ***			X						
Informed consent***				X					
Interventions									
Intervention arm: Family Support Intervention incl. intervention log					X	X	X		
Usual care*	X	X	X	X	X	X			
Assessments*									
Patient demographics, health & functional status, care utilization****				X	X	X	X	X	X
Family member demographics, self-perceived health, care utilization					X	X	X	X	X
Satisfaction with care (FS-ICU-24R) (primary endpoint)						X			
Quality of communication (QQPPI-14)						X			
Nurse support (ICE-FPSQ-14)						X			
Family functioning (FAD-GF-12)					X	X	X	X	X
Family resilience (BRS-6)					X	X	X	X	X
Distress Thermometer (DT)					X	X	X	X	X
Depression & Anxiety (HADS-14)					X	X	X	X	X
Posttraumatic stress (IES-6)					X	X	X	X	X
Life satisfaction (SWLS-5)					X	X	X	X	X
Well-being (WHO-5, QoL-VAS)					X	X	X	X	X

EOT = End of Treatment, EOS = End of Study, FU = Follow-up, Tx = Assessment Timepoint,
*identical for intervention and control arm, ** delegated & designated members of the clinical team, *** study coordinator, **** T0-T1 from clinical record, T2-T4 family member reported

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

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2 ETHICAL AND REGULARY ASPECTS

Before this study will be conducted, the protocol, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements for formal approval.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from the CEC has been received.

2.1 Study Registration

The study will be registered in the Swiss Federal Complementary Database („Portal“) and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov).

2.2 Categorization of the Study

Other Clinical Trial Category A: The health-related study intervention entails only minimal risks and burdens and is prepared in accordance with internationally accepted guidelines, but lacks sound evidence around effectiveness. The intervention consists of nurse- and physician-delivered communication and support interventions, administered through conversations. Data collection involves a series of surveys consisting of validated instruments.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for the clinical trial. The reporting duties and allowed time frame are respected. No substantial amendments are made to the protocol without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9..The following ethics committees are responsible for this trial (cantonal responsibilities in parentheses):

- Ethikkommission Zürich (GL, GR, SH, ZH): http://www.kek.zh.ch/ (Lead)
- Kantonale Ethikkommission Bern (BE, FR – German speaking part, VS – German speaking part): https://www.gef.be.ch/gef/de/index/direktion/organisation/kek.html
- Ethikkommission Nordwest- und Zentralschweiz EKNZ (AG, BL, BS, JU, LU, NW, OW, SO, SZ, UR, ZG): http://www.eknz.ch/
- Ethikkommission Ostschweiz EKOS (AI, AR, SG, TG): https://www.sg.ch/gesundheit-soziales/gesundheit/gremien.html

2.4 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss competent authority’s requirements.

The CEC will receive annual safety reports and interim reports and will be informed about non-substantial amendments, the course of the study, and the study stop / end in agreement with local requirements.

2.5 Declaration of Interest

We declare that there is no conflict of interest.

2.6 Participant Information and Informed Consent

The investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary, and that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or the treatment of his or her close other.

All participants of this study will be provided with a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation.

The participant information sheet and the consent form will be submitted with the protocol for review and approval of the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee), and it will be retained as part of the study records.

Participants in this study are family members of critically ill patients. Critically ill patients are **not** study participants, but their routine clinical data will be extracted for study purposes. In addition, information on patient status, such as re-admission to hospital or death, will be obtained from the participating family members during the study follow-up period.

As critically ill patients are, for the most part, cognitively unable to consent to their clinical data being used for this study upon ICU admission, the eligible family member of the critically ill patient will be informed. S/he will provide his or her written informed consent for the extraction of routine clinical data based on the presumed will of the critically ill patient.

As soon as the critically ill patient regains his or her ability of judgement, his or her written informed consent will be obtained for the extraction of clinical routine data for this study, including family member participant-provided information on his or her health status during study follow-up.

The patient informed consent form (for extraction of routine clinical data) will be obtained through research staff directly from patients. If this is not possible or feasible (i.e. patient has been transferred to a different hospital), participating family members might be asked to act as intermediary.

If patients already have a valid and signed informed general consent form upon ICU admission, no study-specific patient informed consent form will be obtained.

In the event of persistent cognitive inability to sign an informed consent or patient death before his or her signing the informed consent form, the initially provided, surrogate informed consent by family members will be taken as final and valid surrogate informed consent for the use of clinical data of the patient, based on his or her presumed will.

2.7 Participant Privacy and Confidentiality

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially. Any passing-on of information to persons that are not directly involved in the study must be approved by the owner of the information.

Data generation, transmission, archiving and analysis of personal data within this study strictly follows the current Swiss legal requirements for data protection. Prerequisite is the voluntary approval of the participant given by signing the informed consent document prior to the start of his/her participation in the clinical trial.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant's confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare, if the participant has given his/her written consent to do so.

Data generated as a result of this study are to be available for inspection on request by the monitors and by the CEC.

2.8 Early Termination of the Study

The Sponsor-Coordinating Investigator (and competent authority) may discontinue the study prematurely according to certain circumstances:

- ethical concerns,
- insufficient participant recruitment.

2.9 Protocol Amendments

Substantial amendments (significant changes) are only implemented after approval by the CEC.

Significant changes to be authorized by the CEC are the following:

- changes affecting the participants' safety and health, or their rights and obligations;
- changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints, or the form of statistical analysis;
- a change of trial site, or conducting the clinical trial at an additional site; or
- a change of sponsor, coordinating investigator or investigator responsible at a trial site.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human participants may proceed without prior approval of the Sponsor and the CEC. Such deviations shall be documented and reported to the Sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3 INTRODUCTION

3.1 Background and Rationale

Family members are important to the well-being and recovery of critically ill persons yet are profoundly affected by the critical illness themselves (Eggenberger and Nelms, 2007, Hopkins, 2018). During a close other's treatment in an intensive care unit (ICU), families experience high levels of stress and uncertainty, which often negatively affects their coping ability and mental health (Alfheim et al., 2018, Minton et al., 2019, Turner-Cobb et al., 2016), particularly in the event of surrogate decision-making and loss (Azoulay et al., 2005, Siegel et al., 2008). Research reports that 20-60% of family members experience subsequent adverse mental health outcomes, such as symptoms of anxiety, depression, posttraumatic stress, and complicated grief, also known as post-intensive care syndrome – family (PICS-F) (Davidson et al., 2012, Harvey and Davidson, 2011, Kentish-Barnes et al., 2009, McAdam and Puntillo, 2009, van Beusekom et al., 2016).

Such adverse family responses to critical illness have been associated with insufficient quality of family care during ICU (Serrano et al., 2019). Poor communication, insufficient shared decision-making and a lack of emotional and practical support have been found to negatively impact family well-being and health (Gries et al., 2010, Hunziker et al., 2012, Rusinova et al., 2014, Schwarzkopf et al., 2013). Satisfaction with ICU care has been associated with psychological distress (Rusinova et al., 2014), with families who had higher satisfaction levels reporting fewer symptoms (Naef et al., 2021). Family dissatisfaction has been related to a lack of nurse competency, concern and caring by ICU staff, incomplete information and communication, as well as inadequate involvement in decision-making or support (Hunziker et al., 2012, Schwarzkopf et al., 2013). Hence, insufficient quality of family care, such as a lack of engagement and support, coupled with acute stress, not only increases family suffering, but affects family members' functioning in everyday life, and limits their ability to engage in caregiving activities needed by the survivor of critical illness or to cope with their loss (Inoue et al., 2019, Serrano et al., 2019, Torres et al., 2015, van Beusekom et al., 2016, Wintermann et al., 2019).

Research indicates that families of ICU patients have three areas of support needs (Khalaila, 2013, Nagl-Cupal et al., 2012, Olding et al., 2016). First, they need ongoing, clear and consistent communication about their close other's condition and prognosis, especially so when decisions about treatment withdrawal need to be made and a shift from curative interventions to palliation occurs within a short timeframe (Kisorio and Langley, 2016, Nelson et al., 2010, Wong et al., 2015). Second, families want to be present and close to their critically ill family member and partake in the planning and decision-making around care and treatment (Blom et al., 2013, Noome et al., 2016, Vandall-Walker and Clark, 2011). Third, family members require support for dealing with difficult emotions, uncertainty, and stress, for mobilizing resources to live through the event and its aftermath, and eventually for meaning-making of the critical illness and/or death (Cypress, 2011, Frivold et al., 2016). Families whose needs are met report higher satisfaction with as well as increased quality of ICU care (Bailey et al., 2010, Khalaila, 2013, Scott et al., 2019).

The impact of critical illness on family member health and well-being is gaining recognition (Harvey and Davidson, 2011, Netzer, 2018, Rawal et al., 2017). However, many ICUs, while attempting to be more inclusive of family members in care planning and decision making, lack the knowledge, skill, or capacity to provide comprehensive support to families (Kleinpell et al., 2018, Kleinpell et al., 2019). Moreover, hospital policies often fail to recognize the importance of families to safety and quality of care (Hetland et al., 2018). Negative care experiences have been shown to increase the emotional burden that patients and their families face (Agard et al., 2019, Park et al., 2018). The considerable prevalence of post-intensive care syndrome in patients and their families (Inoue et al., 2019), which impacts negatively on their ability to recover and maintain a normal life, requires new models of care delivery that strengthen individuals and families in their

self-care and illness management abilities while also promoting their quality of life (Gerritsen et al., 2017).

While an abundance of research exists around how to better address families' needs during critical illness, empirical knowledge about the effectiveness and successful implementation of new models of care, such as a nurse-delivered and coordinated interprofessional family care pathway, is urgently needed. In Switzerland, clinical research around ICU care delivery to families and on the effectiveness of systemic family nursing interventions is underdeveloped. Inclusive, comprehensive and collaborative models of care delivery for persons living with multimorbidity that promote people's health literacy and improve quality of care have been defined as two of the eight objectives of the Swiss Federal Council's 2030 health policy strategy (The Federal Council, 2019). High-level evidence about nursing interventions and interprofessional models of care delivery in ICU that are effective in improving health and well-being is therefore urgently needed for research-informed health care planning that addresses family needs and improves their health outcomes.

The FICUS trial builds on prior phases of intervention development, feasibility and pilot testing, to now assess intervention effectiveness and to generate data on determinants of successful implementation (Craig et al., 2008). The aims of the intervention are 1) to increase the quality of interaction and communication between families and the ICU team and 2) to improve ICU team's capacity to provide necessary care and support to families. The intervention also seeks 3) to strengthen family illness management capacity and well-being, and 4) to alleviate the impact of the critical illness and / or loss on family members' mental health (see also Figure 2). In a subsequent phase, focus will need to be placed on effective translation of the generated evidence around family support in ICU. Such knowledge will be required to better understand how evidence can be effectively and rapidly translated into routine clinical practice (Brown et al., 2017, Kleinman and Mold, 2009).

3.2 Study Intervention and Indication

To better address families' needs for support, to alleviate their burden, and to reduce the risk for adverse mental health outcomes for family members of patients treated in ICU, international guidelines recommend proactive family engagement, communication and support and the use of specific family support roles and specialist consultations in ICU (Davidson et al., 2017, Kleinpell et al., 2018, Marra et al., 2017, Mitchell et al., 2015). We propose that a protocolized, multi-component, nurse-led family support intervention will increase quality of family care in ICU; that is, families' satisfaction with decision-making processes and the care provided to their critically ill family members and to themselves. In particular, we expect that the intervention will increase the quality of communication and families' support experience in ICU. Systemic interventions that address families' needs for communication and emotional/practical support should increase families' ability to understand and cope with the critical illness and its aftermath. When such intra-family resources and self-care abilities are strengthened by an intervention, families will experience greater mastery and ability to manage the impact of critical illness, loss, or rehabilitation, thereby reducing the negative ramifications of the critical illness on their own mental health.

3.3 Clinical Evidence to Date

Four systematic reviews identified an overall beneficial impact of protocolized family support interventions in ICU (Goldfarb et al., 2017, Lee et al., 2019, Scheunemann et al., 2011, Zante et al., 2020). A significant reduction in ICU stay could be established by two meta-analyses (Goldfarb et al., 2017, Lee et al., 2019), but the evidence on their effect on quality of care and mental health is less clear (Scheunemann et al., 2011, Zante et al., 2020). Studies that tested protocolized

family support interventions with a specific family support role have demonstrated an increase in satisfaction with care and in quality of communication (Moore et al., 2012, Shelton et al., 2010, White et al., 2018, White et al., 2012). However, the effectiveness of such interventions to reduce symptoms of posttraumatic stress, anxiety or depression remains inconclusive (Amass et al., 2019, Curtis et al., 2016, Torke et al., 2016, White et al., 2018). While Curtis et al. (2016) found a decrease in depressive symptoms six-month post-ICU only, White et al. (2018) did not identify a clear trend. The effect on family management ability and functioning has scarcely been investigated (Ågren et al., 2019). The other studies were small feasibility and pilot tests not designed to make inferences about effectiveness.

Hence, the actual evidence base around protocolized family support interventions is modest and requires further substantiation (Zante et al., 2020). Research to date stems predominantly from the US, and only two research groups tested their family support interventions using a randomized design with adequate power (Curtis et al., 2016, White et al., 2018). White and colleagues (2018, 2012), for example developed two different multicomponent nurse-delivered family support interventions (PARTNER & FOUR SUPPORT) for family members of incapacitated patients involved in surrogate decision-making. For the same target group, Curtis et al. (2012) and Curtis et al. (2016) tested a communication facilitator intervention. Two small, non-randomized studies tested family navigator (Torke et al., 2016) or family support coordinator roles (Moore et al., 2012, Shelton et al., 2010) for a more general ICU population. Two RCTs are currently underway in the US and France investigating specialist-delivered family support (Seaman et al., 2018) and a physician-driven support during death and dying (Kentish-Barnes et al., 2018).

3.4 Justification of Study Intervention

We have undertaken pilot and feasibility-testing of a guideline-based nurse-led family support intervention in one ICU in Switzerland (Naef et al., 2020, Naef et al., 2021). This intervention differed from the aforementioned as it added a systemic, advanced family nursing intervention component to the facilitation of interaction, communication, and shared decision-making between families and ICU teams and extended the continuity of engagement from admission into the post-ICU phase. Our mixed methods study established the feasibility and acceptability of the intervention for families and ICU staff (Naef et al., 2020). The before-and-after comparison found that families who received the intervention, in comparison to those who did not, reported higher satisfaction levels with ICU care (difference of 5.54, 95% CI: -0.11 to 11.20), particularly in relation to decision-making (7.26, 95% CI: 0.89 to 13.63), which reached statistical significance (Naef et al., 2021). Qualitative evaluation showed self-perceived benefits for family management of critical illness and its aftermath when the intervention is initiated shortly after ICU admission, is responsive to families' unique needs, and is perceived to be delivered with high proficiency. Nevertheless, we were unable to demonstrate a favorable impact on post-ICU psychological distress, possibly due to design constraints.

Having established acceptability, feasibility, and safety / potential benefit of the above-described guideline-based nurse-led family support intervention, rigorous, real-world evidence generated by a randomized controlled design is now necessary to establish its effectiveness. The pre-existing evidence base around protocolized family support interventions, which is moderate at best, requires further substantiation. Data-based insight around successful implementation of such family support interventions is also needed to prepare rapid translation, should the intervention be proven to be effective. Therefore, the here proposed trial seeks to generate high-quality evidence on intervention effectiveness while also generating knowledge around implementation determinants and strategies of a guideline-based, nurse-led family support intervention in ICU (FICUS Trial).

3.5 Choice of Comparator

We choose usual care provided by ICU nurses and physicians to families as the comparator to the study intervention because routine care delivery to families requires improvement. In addition, it would be unethical and unfeasible to withhold care from family members on control units.

3.6 Risk / Benefits

No adverse effects or specific risks are expected from the intervention. The intervention is based on recommendations; and, as the preliminary study has shown, is acceptable and beneficial to family members (Naef et al., 2020, Naef et al., 2021). Nevertheless, family members of critically ill patients are often in a vulnerable situation, facing high stress levels, with some also experiencing the loss of their close other. Therefore, a cautious approach to the study processes and intervention will be crucial.

Careful attention has been given to recruitment and data collection processes. Family member representatives (see section 6.4) have been involved in the design of the data collection processes and selection of the outcome measures / instruments to be used in this study. Patient / family member representatives will contribute to the design and testing of the case report form (CRF) to ensure that study processes are acceptable and feasible for participants, as well as to the training of study coordinators and interventionists.

3.7 Study Population

The trial will include family members of critically ill persons who receive treatment in an ICU that has been certified by the Swiss Society of Intensive Medicine (SGI), and which is located in major hospitals that operate as regional or specialist centers in the German-speaking part of Switzerland. Critically ill persons are defined as those with an expected length of stay in ICU of 48 hours or longer, combined with a life-threatening condition with a high risk of death or long-lasting functional impairment, or a high risk of prolonged mechanical ventilation (>24 hours). Family members are defined as close others from the patient's perspective, as noted in clinical records or advanced directives, or as legally defined surrogate decision-makers.

Participants in this study are family members. They have to be a primary support person of the critically ill patient, of full age (≥18 years), able to complete the baseline data collection and family-reported questionnaires in German language, and sign a written informed consent.

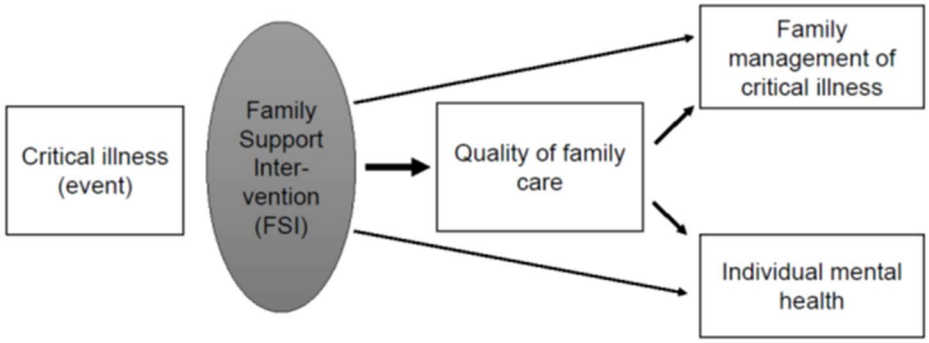
Critically ill patients are **not** study participants. However, routinely collected clinical data will be extracted in order to be able to describe the sample. Please see section 2.6 for more detail.

4 STUDY OBJECTIVES

4.1 Overall Objective

The aim of the trial is to investigate the effectiveness of a guideline-based, nurse-led, interprofessional family support intervention (FSI), consisting of a family nursing role and family care pathway in intensive care units, on quality of family care, family management of critical illness, and mental health of the index individual family member (see Figure 1). In addition, implementation barriers / enablers will be identified.

Figure 1: Intervention mechanism



4.2 Primary Objective

The primary objective is to test the effect of the FSI on quality of family care in ICU in comparison to usual care in index family members of critically ill patients.

Hypothesis 1: Compared to usual care, the FSI will increase the quality of family care - i.e. satisfaction with ICU care (H1) reported by family members after patient discharge / death.

4.3 Secondary Objectives

The secondary objective is to test the effect of the FSI on further indicators of quality of care, family management of critical illness, and index family members' post-ICU mental health in comparison to usual care.

Hypothesis 2: Compared to usual care, the FSI will increase the quality of communication (H2a) and nurse support (H2b) reported by family members after patient discharge / death.

Hypothesis 3: Compared to usual care, the FSI will improve family management of critical illness (H3a) and individual well-being (H3b) but decrease symptoms of psychological distress (H3c).

Hypothesis 4: Psychological distress will decrease over the long-term (H4a) whereas individual well-being (H4b) and family management abilities will improve (H4c).

It is a further objective to investigate the real-world context in which the study intervention is implemented to discern determinants and strategies of implementation success. As this objective is explorative, a research question instead of a hypothesis is formulated: What contextual factors and strategies enable or impede successful implementation of the family support intervention in ICU?

4.4 Safety Objectives

Not applicable.

5 STUDY OUTCOMES

5.1 Primary Outcome

The primary study outcome is quality of family care in ICU, operationalized as family satisfaction with ICU care, which is an established core indicator of quality of family care (Kentish-Barnes et al., 2009, Padilla Fortunatti and Rojas Silva, 2018, Scott et al., 2019). It will be assessed at the individual participant level at discharge from ICU (T1) by the FS-ICU-24R transformed mean score ranging from 0 to 100.

5.2 Secondary Outcomes

Quality of family care is further operationalized with the secondary outcomes of quality of communication and nurse support, assessed at discharge from ICU (T1) by the Questionnaire on Quality of Physician-Patient Interaction (QQPPI-14) and the Family Perceived Support Questionnaire (ICE-FPSQ-14).

Family management of critical illness was also chosen as a secondary outcome. It will be assessed by the Family Assessment Device General Functioning Scale (FAD-GF-12) and the Brief Resilience Scale (BRS-6).

Mental health – covering the spectrum from well-being to psychological distress – was chosen as a further secondary outcome. Subjective well-being will be measured by the Satisfaction with Life Scale (SWLS-5), the WHO-5 Well-Being Index (WHO-5), and an adapted VAS on general quality of life (QoL-VAS). Psychological distress will be assessed with the Distress Thermometer (DT), the Impact of Events Scale-6 (IES-6), and the Hospital Anxiety and Depression Scale (HADS-14).

All secondary individual-level outcomes concerning family management and mental health will be measured at baseline (T0), at discharge from ICU (T1), as well as at three follow-up time points (three, six-, and twelve-months following discharge). Table 3 provides an overview of the individual-level study outcomes.

Quality of family care was chosen as the primary outcome because it is directly amendable by the family support intervention. It has also been associated with family member mental health outcomes, suggesting that those who report higher levels of satisfaction and quality of support experience lower levels of psychological distress (Naef et al., 2021, Rusinova et al., 2014). Family management was chosen as a secondary outcome since the intervention also targets families' ability to cope with critical illness as a family. Mental health and family management are more distal than quality of family care, but highly relevant outcomes of interventions that address families' needs for support and promote family capacity and health (Cameron et al., 2016, Stepanovic et al., 2018).

Table 3: Overview of individual-level study outcomes

Domain / Construct	Measure*	Analysis metric	Method of aggregation	T0	T1	T2	T3	T4
Quality of Family Care								
Satisfaction with care (primary outcome)	Family satisfaction with ICU Care (FS-ICU-24R)	Final value (0-100)	Mean		X			
Quality of communication	Questionnaire on Quality of Physician-Patient Interaction (QQPPI-14)	Final value (1-5)	Mean		X			
Support from nurses	Family Perceived Support Questionnaire (ICE-FPSQ-14)	Final value (14-70)	Sum		X			
Family Management								
Family functioning	Family Assessment Device - General Functioning Scale (FAD-GF-12)	Final value (1-4)	Mean	X	X	X	X	X
Family resilience	Brief Resilience Scale (BRS-6)**	Final value (1-5)	Mean	X	X	X	X	X
Mental Health								
Subjective well-being	Satisfaction with Life Scale (SWLS-5)	Final value (5-35)	Sum	X	X	X	X	X
	WHO-5 Well-Being Index (WHO-5)	Final value (0-100)	Sum	X	X	X	X	X
	Adapted VAS on Quality of Life (QoL-VAS)	Final value (0-100)	None	X	X	X	X	X
Psychological distress	Distress Thermometer (DT)	Final value (0-10)	None	X	X	X	X	X
	Impact of Events Scale-6 (IES-6)	Final value (0-4)	Mean	X	X	X	X	X
	Hospital Anxiety and Depression Scale (HADS-14)	Final value (0-21)	Sum	X	X	X	X	X

* use of German versions of measures, ** adapted for family

5.3 Safety Outcomes

Not applicable.

6 STUDY DESIGN AND COURSE OF STUDY

6.1 General Study Design and Justification of the Design

The FICUS trial is designed as a parallel cluster randomized, controlled, multicenter superiority trial with equal numbers of clusters per study arm and a primary endpoint of quality of family care in ICU, assessed after patient ICU discharge or death. Cluster randomization is necessary as the family support intervention (FSI) will be introduced and integrated into interprofessional ICU care delivery processes (Campbell, 2014, Campbell et al., 2012, Donner and Klar, 2010, Gums et al.,

2016). The study aim requires a pragmatic approach to the trial design in order to generate evidence that is relevant to the clinical context in which the intervention will eventually be implemented if proven effective (Loudon et al., 2015). The design of the FICUS trial is consistent with practice-based health services research (Kleinman and Mold, 2009), whereby trained individuals from the clinical setting deliver the intervention under ongoing supervision by the researchers (Brown et al., 2017).

The FICUS trial has a dual focus on effectiveness and implementation (Curran et al., 2012). First, and primarily, the trial is designed to establish whether the FSI will be effective under real-world conditions. Second, using an embedded case study approach, it will explore implementation context and strategies on intervention units. To do so, we will employ a hybrid design type I in which, alongside with clinical effectiveness, contextual determinants (barriers / facilitators) of and potentially successful strategies for implementation are also explored. The use of effectiveness-implementation hybrid designs (Curran et al., 2012) is fitting when the aim is to not only test if a program works in clinical practice but to explore how it could work, or how it could best be implemented within routine ICU care delivery once proven effective, thereby exploring context and process of the intervention delivery and implementation simultaneously (Brown et al., 2017, Moore et al., 2015). This is necessary to enable rapid translation of evidence into clinical practice.

According to the Medical Research Council (MRC) framework for the development and testing of complex interventions, which are interventions that contain several interacting components, our study aligns with the evaluation or type III phase in which effectiveness is assessed (Craig et al., 2008, Lovell et al., 2008). The FICUS trial will also stretch into phase four during which implementation context and strategies are explored to determine how the intervention could be successfully adapted and scaled-up in slightly different contexts (Aarons et al., 2017).

The participating clusters (ICUs) will be assigned to the intervention or control group by minimization regarding the degree of specialization (specialized vs. general ICU) and the hospital (as some participating ICUs will be from the same hospital). After the first cluster having been randomly assigned, a random component of 10% will be introduced into the minimization algorithm of the following clusters to prevent fully deterministic assignment. The assignment will be performed after recruitment of the clusters.

To reduce potential imbalance of study groups at baseline, restricted randomization with a 1:1 allocation will be used (Esserman et al., 2016, Ivers et al., 2012). Clusters assigned to the intervention arm will implement a guideline-based, nurse-led family support intervention (FSI), which will be delivered to family members of patients in ICU by family nurses and ICU physicians. Family encounters and brief interactions (lasting 5-15 minutes) as well as therapeutic family conversations and interprofessional family meetings (30-60 minutes) will be conducted by the family nurse, whereas family meetings will be conducted jointly by the family nurse and an ICU physician.

Family members of patients in clusters (ICUs) of the control group will be provided with usual care, which is defined as a non-protocolized approach to family care and services offered by nurses, physicians, teams, or other health professionals that are an established part of the ICU's routine care delivery before trial start and will be assessed at each study unit before recruitment launch.

According to the approach described by Hemming et al. (2017), a cluster size of 47 participants (family members) is sufficient given 8 clusters per study arm, an intra-cluster correlation coefficient (ICC) of 0.03, and a coefficient of variation in cluster size of 0.2, taking into account that due to the design effect (Kerry and Bland, 1998), the number of participants required for our cluster-randomized trial is bigger than the sample size of a standard RCT. The calculation is based on a difference in FS-ICU-24R total score between intervention and control groups of 5.5 and a within-group standard deviation of 16.3, as it was observed in a previous study (Naef et al., 2021). However, power calculations for different numbers of clusters per condition, mean cluster sizes, and inter-cluster correlation coefficients showed that to achieve a power 0.8 and account

for a drop-out rate of 10 % among individual participants (no dropouts of clusters), an average number of 56 patients should be recruited per cluster. Therefore, the projected sample size is 896 participants (family members).

6.2 Study Duration and Study Schedule

Table 4 shows the study schedule over 42 months. Table 1 (page 33) lists the cluster timeline and Table 2 (page 34) shows the individual participant timeline.

Table 4: Study schedule

Months	**1-6**	**7-12**	**13-18**	**19-24**	**25-30**	**31-36**	**37-42**
Preparatory phase: 6 months							
Recruitment: 18 months							
# of patients recruited 896 total	-	299	299	299	-	-	-
Follow-up: 12 months per patient							
Analysis: 6 months							

6.3 Methods of Minimizing Bias

6.3.1 Randomization

The allocation sequence for the participating clusters (ICUs) will be generated using minimization. Variables used in the minimization procedure are the degree of specialization (specialized vs. general ICU) and center (from some centers, several ICUs will participate). To avoid the minimization to be fully deterministic, we will use a random component of 10 %. Minimization will be used on all ICUs which participate at the start of the study (in alphabetical order) and may be used to allocate ICUs which decide to participate later. Centers will be recruited before being allocated to intervention or control. As the allocation is determined after recruitment of clusters, with the first ICU being allocated randomly and all subsequent ICUs with a random element in the minimization procedure, allocation is not predictable. The cluster allocation sequence will be generated by the Trial Statistician, Stefanie von Felten, using the R package *Minirand* (Jin et al., 2020).

6.3.2 Blinding

Blinding of study participants and care provides will not be possible due to the nature of the study intervention. As this is a cluster RCT, blinding of the data assessors is not feasible.

6.3.3 Retention

To promote retention at the cluster level, the research team will provide quarterly communication via newsletters on study progress, next steps in the study and an appreciation of the efforts made, to study ICUs and leadership. We will also interact regularly with the local study team and site.

To ensure retention of individual study participants, local study teams will make utmost effort to obtain completed questionnaires at admission, discharge, and at the three post-ICU follow-ups at month three, six and twelve, including strategies such as (Calvert et al., 2018):

- Admission and discharge data collection points will involve phone or face-to-face

interactions to facilitate completion of questionnaires during this particularly vulnerable critical illness phase.

- During the post-ICU phase, emails or letters will be sent to family members to inform them about the upcoming follow-up data collection.
- If questionnaires are not completed within two weeks, they will be followed-up by phone every week for 2 weeks. Follow-up calls for data collection reasons will be recorded in the participant list.

In case family members decide to withdraw and discontinue follow-ups, the reason to do so will be recorded in a structured format. Patient survival status will also be obtained.

6.4 Patient and Public Involvement

A patient and family advisory group (PFAG) with five members (1 patient, 3 family members, 1 patient facilitator) ensures that the FICUS trial is relevant and meaningful to critically ill patients and their family members. The PFAG designs study processes to guarantee that participation is feasible and acceptable to family members in ICU (National Institute for Health Research, 2012, National Institute for Health Research, 2017). User involvement in the FICUS trial adopts two approaches. First, an ongoing partnership is formed with the PFAG, with one user as project partner. This person co-designs involvement strategies, co-leads consultation and communication, and acts as a liaison between research team and PFAG. Second, PFAG members give advice, contribute their expertise, and are actively involved in managing the trial as co-designers.

The PFAG began by helping to create a user involvement strategy for the trial, drawing on established frameworks and existing evidence (Burns et al., 2017, Greenhalgh et al., 2019, Pandya-Wood et al., 2017), which defines methods and strategies, user profiles, involvement planning across six research project stages, practical arrangements, recognition of users' participation, and evaluation plans. Past involvement helped develop the research question (Naef et al., 2020) and research proposal. Users have advised on recruitment strategies, data collection processes, study intervention, data collection instruments and dissemination plans, giving feedback on the proposal and co-writing both the lay abstract and this section. This was done through individual consultation (August, October 2020) and a user workshop (September 2020). Additionally, a workshop with providers was held in August 2020. Future involvement will be collaboration during the administrative pre-launch (i.e., preparation of study documents, training of data assessors and interventionists, public communication), recruitment and data collection (i.e., retention procedures, ongoing reflection on study course), data analysis (i.e., interpretation of results, critical review), and dissemination (e.g., planning, dissemination activities, lay summaries, etc.).

7 STUDY POPULATION

7.1 Eligibility Criteria

7.1.1 Study Center and Cluster Eligibility Criteria

The FICUS trial will take place in the German-speaking part of Switzerland. We will choose ICUs in university, cantonal or major hospitals that operate as a regional or specialist center, have been certified by the Swiss Society for Intensive Medicine, run 8 ICU beds or more and have at least

300 admissions per year. An ICU is defined as “an organized system for the provision of care to critically ill patients that provides intensive and specialized medical and nursing care, an enhanced capacity for monitoring, and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency” (Marshall et al., 2017).

Research indicates that families of patients whose critical illness has a high degree of uncertainty and unpredictability, requires surrogate decision-making, and has a high likelihood of death or adverse functional outcomes, have the highest support needs (Inoue et al., 2019). Hence, study ICUs need to be able to offer the highest level of patient care and treat patients who are hemodynamically unstable, require ventilation with multiple-organ failure and need multidisciplinary intervention. They may offer different or combined specialty care, including surgical, trauma, medical, cardiac, or neurological care.

Study ICUs may be located at the same hospital but need to be sufficiently distant from each other to avoid cross-contamination and be staffed by independent (nursing) teams. We will only choose ICUs with at least eight beds to ensure sufficient patient influx to meet recruitment targets within the specified study duration. ICUs possessing a protocolized, interprofessional family communication policy will be excluded.

7.1.2 Patient and Family Member Eligibility Criteria

Potential participants are family members of critically ill persons admitted to a study ICU. A family member is defined as a close other from the patient’s perspective, as noted in the clinical record or in advanced directives, or as indicated by the legally defined, surrogate decision-maker. All family members of a patient are eligible to receive the intervention, but only one family member, either the primary support person or surrogate decision-maker, will be enrolled in the study. Family members must provide written, informed consent prior to any data collection.

7.1.2.1 Inclusion Criteria

Family members of patients fulfilling the following criteria may be invited for study participation (=patient-related eligibility criteria):

- Expected length of stay in ICU ≥48 hours, as predicted by the intaking ICU clinician (physician or nurse) within 24 hours of admission.
  AND
- Life-threatening condition with a high risk of death or long-lasting functional impairment OR high risk of prolonged mechanical ventilation (>24 hours).

Family members fulfilling *all* of the following inclusion criteria are eligible to participate in the study:

- Primary support person of the patient.
- Able to complete family-reported outcome measures (questionnaires) in German language.
- Age ≥18 years.
- Signed informed consent form.

7.1.2.2 Exclusion Criteria

The presence of any of the following patient-related exclusion criteria will lead to ineligibility of family members:

- Preexisting declined general consent.
- ICU stay <48 hours.

The presence of any one of the following exclusion criteria will lead to exclusion of a family member:

- Prior inclusion in FICUS trial on another study ICU.
- Cognitive inability to understand the study or complete the questionnaire as appraised by clinicians and / or study recruitment staff.
- Inability to complete baseline data collection within the required time frame after admission / study enrollment (Calvert et al., 2018).

7.2 Recruitment and Screening

7.2.1 Recruitment Strategies

Each ICU was chosen based on their number of ICU beds (minimum of 8) and number of admissions per year (minimum of 300) to ensure sufficient capacity to meet the recruitment targets of 56 participants within 18 months.

Eligible family member participants will be recruited after patient admission to ICU. Study centers will perform daily eligibility screening of newly admitted patients and potential family member participants. Screening will be carried out based on available clinical data and expert judgement.

Study eligibility based on patient-related inclusion criteria will first be assessed by the intaking clinician (nurse or physician) or a designated team of clinicians, who will also obtain contact details of at least one family member (if available). If feasible, the clinician provides initial information about the study and hands out a study flyer and information to family members. Study flyers will also be displayed in the waiting area and included in ICU information packages routinely handed to family members. Written study information will also be available on websites. In a next step, the study coordinator will contact eligible family members per phone or in-person when they visit their critically ill close other, explain the study, and invite participation. Family members will be given time to decide on their participation in accordance with ethical guidelines.

Participants do not receive payment or other forms of compensation. A thank you letter will be written to them upon study completion.

7.2.2 Feasibility of Recruitment

Study centers undertook retrospective analysis of patients admitted to their ICU during the preceding year using their minimal data sets. Based on this data, approximately 6509 admission (not patients) per year with an ICU stay of 48 hours or longer were recorded. Study centers' estimates indicate that in around 30% of these admissions, patients will have a family member who meets the inclusion criteria (cognitive ability, language requirement, completion of questionnaire within required timeframe), forming a pool of 1966 eligible participants per year to recruit from.

Based on our experience with recruitment of family members in ICU, projections tend to be too optimistic. Not all family members will provide informed consent. Feasibility of recruitment may also be challenged by the unpredictability of the current COVID-19 pandemic. The pandemic has revealed the necessity of family engagement and support during critical illness and has prompted the use of technology to maintain communication (Negro et al., 2020, Rose et al., 2020). Since the first outbreak, ICUs have increased their preparedness and ability to respond to COVID-19 surges (Aziz et al., 2020). Given the trial design and intervention (i.e. use of communication technology and electronic data capture, support for staff and family), it is expected that recruitment and intervention delivery will remain feasible, although reduced, during waves of the pandemic (Newcomb et al., 2020). If necessary, recruitment will be paused. However, it is important to plan for sufficient time for participant recruitment, also given that not all eligible family members will give informed consent. Therefore, we project a recruitment period of 18 months.

7.3 Assignment to Study Groups

Cluster randomization is necessary when the intervention is part of team-based care delivery, when interdependence is present or when it is more ethical to offer an intervention to all members within a group, which all apply in the FICUS trial (Esserman et al., 2016).

7.3.1 Allocation Sequence

The allocation sequence for the participating clusters (ICUs) will be generated using minimization at a central location (Zurich, Switzerland). Variables used in the minimization procedure are the degree of specialization (specialized vs. general ICU) and the hospital / center (from some centers, several ICUs will participate). To avoid the minimization to be fully deterministic, we will use a random component of 10 %. Minimization will be used on all ICUs which participate at the start of the study (in alphabetical order) and may be used to allocate ICUs which decide to participate later.

7.3.2 Concealment Mechanism

Clusters will be recruited before being allocated to intervention or control. As the allocation is determined after recruitment of clusters, with the first ICU being allocated randomly and all subsequent ICUs with a random element in the minimization procedure, allocation is not predictable. Allocation will be revealed to study centres after cluster-level baseline data have been obtained. This is necessary to enable intervention clusters to recruit interventionists from their teams, who will then be trained before participant enrollment begins.

7.3.3 Implementation

Clusters will be identified and enrolled by the Sponsor-Coordinating Investigator. The cluster allocation sequence will be generated by the trial statistician, Stefanie von Felten, using the R package *Minirand* (Jin et al., 2020). All eligible participants at one of the study ICUs who signed an informed consent form will be enrolled consecutively in the study.

7.4 Criteria for Withdrawal/ Discontinuation of Participants

The intervention and the data collection will be discontinued if a family member withdraws consent. The data of the last completed assessment timepoint will be included in the analysis (as per intention-to-treat analysis).

8 STUDY INTERVENTION

8.1 General Information

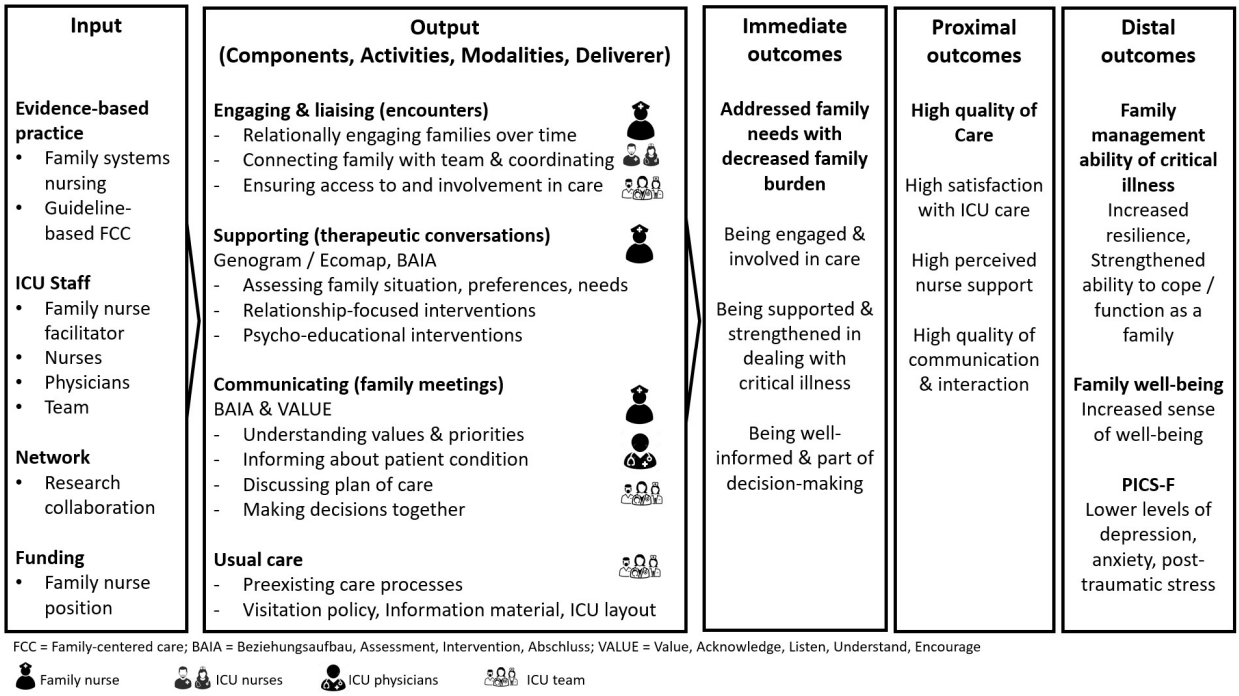
8.1.1 Study Intervention

The study intervention has been slightly adapted from our pilot study (Naef et al., 2020, Naef et al., 2021) in consultation with 5 user representatives, 7 nurses and 3 physicians to increase the feasibility of intervention implementation across the different study ICUs while maintaining core components (Movsisyan et al., 2019). Figure 2 illustrates the Program Logic Model of the family support intervention (FSI).

Study Intervention A

- Family support intervention (FSI)

Figure 2: Program Logic Model of FSI



8.1.2 Control Intervention

Usual care will serve as the comparator in this study. It is defined as a non-protocolized approach to family care and services offered by nurses, physicians, teams, or other health professionals that are an established part of the ICU's routine care delivery before trial start. These include granting access (visitation), interacting with family members and informing about the patient's condition and treatment (written and oral information), communicating with family members as surrogate decision-makers (communication structure), supporting families (support structures), and making referrals (auxiliary services). ICU staff in the control units will be allowed to act upon patient / family needs. However, the introduction of a new protocolized family support program or approach to care, a family nursing or other family support role, and of a structured family support pathway is not permitted. "Usual care" will be assessed with a standardized score sheet at each study unit before recruitment launch.

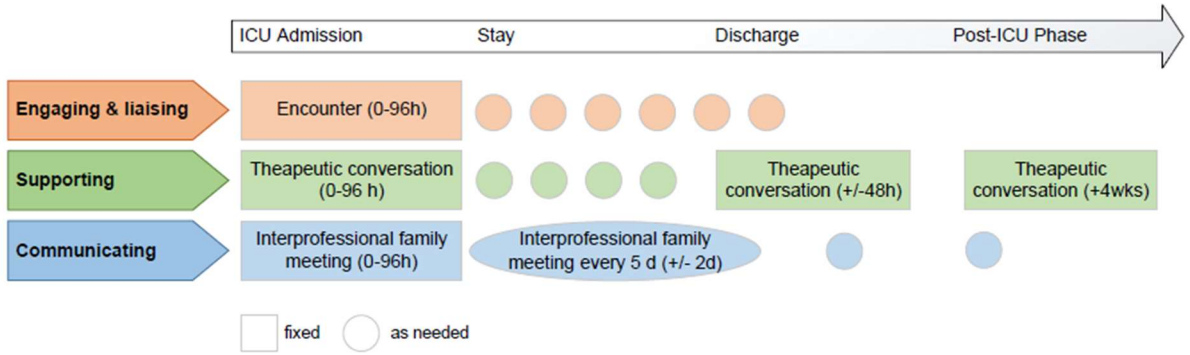
8.2 Administration of Study Intervention

8.2.1 Study Intervention

The family support intervention (FSI) is grounded in a family systems nursing approach (Doane and Varcoe, 2005, Gottlieb, 2012, Rolland et al., 2017, Wright and Leahey, 2013). A family systems approach proposes that critical illness affects families' affective, cognitive, and behavioral functioning, requiring therapeutic relational nurse-family engagement, including relationship-focused and psycho-educational interventions to support family management of illness and to alleviate their suffering. We utilize evidence around systemic family interventions for chronic illness (Chesla, 2010, Hartmann et al., 2010, Mahrer-Imhof and Bruylands, 2014, Östlund and Persson, 2014), which suggests that the use of a combination of psycho-educational and relationship-focused interventions is most effective in strengthening family and individual

health and well-being. The FSI also builds on guideline-based recommendations around ICU care to families (Davidson et al., 2017) that include the use of a specific family consultation role and of structured, interprofessional communication with families to ensure high quality of family care. Hence, the FSI consists of a new family nursing role which delivers three interacting, closely intertwined intervention components that are mapped to a family care pathway (see Figure 3 and Table 5).

Figure 3: Family care pathway



Component 1 - Engaging & liaising: This intervention component involves relationship-building with families, connecting and coordinating family care activities as well as transition and follow-up care for family members and surviving patients. It is delivered by the ICU family nurse in close collaboration and together with health professionals, particularly ICU nurses, involved in the patient's care. It aims to ensure coordinated care through facilitating mutual understanding and enabling participatory interaction between the family and ICU team over time, and to connect families to needed auxiliary services and practical support.

Component 2 - Supporting: This component is based on a relational, family systems nursing approach and includes assessing family structure, processes and resources and supporting families through relationship-focused and psycho-educational interventions at the family systems level. It is delivered by the ICU family nurse and involves activities such as getting to know the family, asking circular and interventive questions, inviting reflection, listening attentively, drawing forth family resources, providing education and counselling, and facilitating family coping strategies. It aims to strengthen family coping, health literacy and illness management and to decrease family suffering.

Component 3 - Communicating: This component focuses on structured, interprofessional communication and shared decision-making with families. The family nurse and a physician co-moderate the meeting and other members of the team participate as required. It aims to clarify patient / family preferences, to provide family with knowledge about the patient situation and expected outcome, and to ensure shared planning and decision-making according to families' preferred involvement.

Intervention components are delivered in three forms. Family encounters are brief interactions lasting 5-15 minutes, whereas therapeutic family conversations and interprofessional family meetings will last around 30-60 minutes. Encounters and therapeutic conversations are delivered by family nurses, whereas family meetings include at least the family nurse and an ICU physician.

Table 5: Intervention activities in each component and along the family care pathway

	Family Care Pathway			
Intervention activities	**Admission to ICU**	**During ICU stay (as needed)**	**Discharge from ICU**	**Post-ICU**
Engaging & Liaising (encounters) Relational engaging Connecting & coordinating Ensuring access over time	Entering into relationship Introducing team and roles Orienting family to ICU & availability	Maintaining relationship Checking in on a regular basis Ensuring consistent and collaboratively coordinated processes of family care	Checking-in Initiating process of relationship termination Supporting transition (transfer out of ICU, dying)	Following-up Making referrals / connecting to community-based services Terminating relationship
Supporting (conversations) Assessing family situation, preferences, & needs Relationship-focused interventions Psycho-educational interventions	Bringing family members together (if possible) Getting to know the family (assessing) Using systemic intervention processes* to provide emotional, cognitive and behavioral support	Sitting down with the family Re-assessing situation and needs Using systemic intervention processes* to provide emotional, cognitive and behavioral support	Working with family to prepare / live through transition / dying Re-assessing situation and needs Using systemic intervention processes* to provide emotional, cognitive and behavioral support	Inquiring about individual and family well-being Re-assessing situation and needs Using systemic intervention processes* to provide emotional, cognitive and behavioral support, with a particular focus on meaning-making of experience
Communicating (meetings) Understanding patient as person, family as family Providing information about patient condition Discussing plan of care Shared decision-making	Listening to families and answering their questions Valuing family experience and perspectives Providing consistent and timely information in a fitting way Discussing preferred way of working together	Listening to families and answering their questions Valuing family experience and perspectives Providing consistent and timely information in a fitting way Discussion treatment aims and plan of care	Listening to families and answering their questions Valuing family experience and perspectives Providing consistent and timely information in a fitting way Making decisions together	Valuing family experience and perspectives Being guided by family questions / concerns Providing information to support understanding and meaning-making

* Encouraging the telling of the family / illness narrative, circular & interventive questioning, attentive listening, offering education and counselling, drawing forth family resources & capacities, enabling family togetherness & rituals, strengthening family self-care and illness management ability

8.2.2 Interventionists

The intervention will be performed by designated family nurses per cluster in close collaboration with the ICU team. Interventionists will be registered nurses with a Swiss certification in ICU nursing or equivalent, or at least two years of clinical experience in ICU care, and training in family systems nursing. They hold a Master of Science in Nursing or work under the supervision of an

advanced practice nurse. Advanced competencies in family nursing (International Family Nursing Association, 2017) are necessary for the following reasons:

- Family vulnerability: Families are in a vulnerable situation and / or crisis, which requires specific knowledge and expertise around family processes and illness management.
- Type of intervention: The relational, systemic family interventions require specific knowledge and skills beyond the general competencies of ICU nurses.
- Role: The role combines clinical practice with families, consultation, collaboration and leadership (Hamric et al., 2014).

Based on our pilot study (Naef et al., 2020), participating family members identified the following interpersonal competencies as key to a supportive relationships with the interventionist:

- Being proactively and discreetly available, being approachable and easy to build trust with
- Being empathic, taking an interest, being calm, asking the right questions
- Acting on eye-level, letting family take the lead
- Being highly competent in terms of critical illness, ICU care and working with families

8.2.3 FSI Implementation Strategies

The FSI will be implemented using the following strategies, which showed promise in the pilot study (Naef et al., 2020), and which will be adopted to the local contexts.

- Interventionist training: Interventionists will receive a five-day introduction to the study intervention and education in systemic family nursing, including communication and therapeutic listening skills. The training will be offered by members of the research team and external family nursing / ICU experts.

- FSI endorsement by ICU leadership: Study investigators will meet with ICU leadership to ensure full support and to discuss strategies for successful team acceptance before study start. The nurse and physician leadership team will inform ICU staff through email and other established channels to endorse the FSI and encourage full engagement.

- Identification of a nurse and physician champion: We will identify a nurse and ICU physician to act as local champions. These champions will take a leadership role in supporting integration of the FSI and the family nursing role into ICU care delivery. They will also work with the research team to address implementation challenges.

- Educating ICU team about FSI: Study investigators will provide ICU staff with a brief written description of the family support pathway, family nursing role and intervention components. They will educate ICU nurses and physicians on-site about the FSI, with a focus on the interprofessionally-delivered intervention components (2-3 sessions per ICU).

- Internal and / or external implementation facilitator: An internal or external implementation facilitator will initially be present daily to support the ICU team and the interventionist in deploying the FSI according to protocol, and then be present at regular intervals. Members of the research team will provide biweekly on-site or online consultation (or as needed), providing coaching and assistance on intervention fidelity and implementation strategies.

- Implementation activity log: A structured implementation activity log will be completed over the course of the active delivery of the intervention by the internal implementation facilitator or local investigator (see Table 1 and section 9.1).

8.2.4 Discontinuation of Intervention

As this is a cluster randomized trial, there will be no individual-level allocation that could be discontinued. However, the intervention will be discontinued if a family member withdraws consent.

8.3 Compliance with Intervention

The intervention is standardized in terms of components, intervention content, and a minimum dose along the clinical patient pathway (i.e. at least five intervention contact / doses, including one encounter, three therapeutic conversations, and one interprofessional family meeting) (Sidani and Braden, 2011). The frequency of intervention contacts and the dose of each intervention component can be increased and tailored according to patient and / or family preferences and needs. Individual patient or family adherence to a particular health behavior is not required. Fidelity to the intervention protocol is ensured at the cluster level. Adherence is promoted as follows:

- Monthly supervision for interventionists: The family nurses delivering the study intervention will receive at least monthly supervision from a study center-based or external advanced practice family nurse involved in the trial. They have access to case-specific consultation and support.
- Case conferences with interventionists: Online, anonymized case conferences with all interventionists across intervention clusters will be held monthly to support consistency and adherence to core components and pre-defined minimum intervention dose and frequency.
- Site visits for quality control of the intervention: A member of the research team will undertake a site visit within the first three months after recruitment launch. This will include an audit of the intervention documentation (at least 10 cases) and an observation of intervention delivery using a predefined list of criteria. Feedback will be provided to interventionists and their supervisors, and an action plan devised if necessary. Further site visits will depend upon the quality level.

8.4 Data Collection and Follow-up for Withdrawn Participants

If participants withdraw consent, the reason for withdrawal will be assessed at the timepoint of withdrawal and – if the participant agrees – data on the clinical status of the patient will be collected (change in health status / or death, timepoint of death). No follow-up is planned.

8.5 Concomitant Intervention(s)

While intervention components are clearly defined, the dose and frequency will be variable and determined based on patient illness course, length of ICU stay, and family needs / preferences. A minimum dose of five interventions has been specified (see Figure 3) and will be delivered within a defined time window along the clinical patient pathway – i.e. within 0-96 hours after admission, 48 hours before or after discharge, and follow-up (up to 4 weeks after discharge / loss). A higher intervention dose or frequency is permitted. Any interaction between ICU shift or primary nurses, ICU, or other treating physicians as well as other health or social care professionals are explicitly permitted. There are no interventions that are prohibited during the study. All interventions delivered by the interventionists will be recorded in the eCRF intervention log (see section 9.2.4). Hence, all concomitant interventions or interventions exceeding usual care have to be recorded.

9 STUDY PROCEDURES

9.1 Assessment of Cluster-Level Data

Clusters that have signed a study agreement will be enrolled and randomly allocated to intervention or control group after cluster-level baseline data collection. Data at the cluster level will be assessed at baseline before randomization, every 12 months, and after the last participant has reached T1 (patient discharge). It will be extracted from policy documents, project partner interviews or self-assessment, and an ICU data set using a standardized electronic extraction tool.

ICU characteristics will be obtained from the most recent Minimal Data Set (MDSi) routinely collected by ICUs according to the standards of the Swiss Society of Intensive Medicine (Table 6).

Quality of family care indicators are based on guidelines for family-centered care in ICU issued by the Society of Critical Care Medicine (Davidson et al., 2017) and will be assessed at the cluster-level using a standardized score sheet provided by the Society of Critical Care Medicine (Hwang et al., 2017) (Table 6). These indicators will allow us to determine the degree to which usual care in relation to families is provided at the ICUs pre-intervention, and they will also allow us to distinguish between usual care and the FSI post-intervention at the cluster level. In addition, the Patient- and Family-Centered Care Organizational Self-Assessment Tool will be used to assess degree of family engagement (Institute for Healthcare Improvement, 2013) (Table 6).

Table 6: Cluster-level data

ICU characteristics based on Minimal Data Set (MDSi)	
Total number of beds (certified & run), total number of patients admitted per year and total number of treatment days	
Percentage of high-risk admissions (% of admissions with SAPS-2 >45) and unplanned admissions	
Percentage of patients in SGI Category level 1a, 1b, 2, 3	
Percentage of patients treated with cardiac, respiratory, central nervous system, abdominal problems & accidents	
Percentage of mechanically ventilated patients & >95 hours of ventilation / >1000 NEMS-Points	
Length of stay (mean)	
Frequency of discharge destination (other ICU, IMC, Unit in same / other hospital, died)	
Full time equivalent of nurses / physicians / other staff	
Staffing level (full time equivalent / number of ICU beds)	
Percentage of staff with ICU certification (nurse / physician) & with training in family nursing / care	
Quality of Family Care indicators	
Category 1: Family presence	
Category 2: Family support	
Category 3: Family communication	
Category 4: Consultations	
Category 5: Operational and environmental issues	
Degree of family engagement	
Domain 1: Leadership & operations	Domain 7: Information / education
Domain 2: Mission, vision, values	Domain 8: Diversity & disparities
Domain 3: Advisors	Domain 9: Charting & documentation
Domain 4: Quality improvement	Domain 10: Care support
Domain 5: Personnel	Domain 11: Care
Domain 6: Environment design	

Implementation activity and cost log: Clusters that are assigned to the study arm will in addition collect information on implementation activities (as described under 8.2.3 and 8.3) and costs in a a structured implementation log.

Implementation strategies (see 8.2.3) used to introduce and maintain fidelity of the intervention will be recorded by the internal implementation facilitator or local investigator in a structured format.

Implementation costs associated with the installment of the intervention at the ICU will be recorded. Cost indicators include (but are not necessarily limited to) implementation of structures and processes, acquisition of staff to deliver the intervention, and intervention-specific training (if not already part of current training schedules). Costs will also be assessed retrospectively for the preparatory study phase (before the start of the first intervention).

Embedded case study: To answer the research question around contextual factors and strategies that enable or impede successful implementation of the FSI as a new model of family care in ICU, a multiple case study will be undertaken (Yin, 2018). For this embedded case study, a separate study protocol will be developed and submitted to the competent ethics committees.

A multiple case study is a fitting methodology to evaluate the implementation of complex interventions (Walshe, 2011). Each case – i.e., an ICU where the FSI was introduced – is studied in-depth followed by a comparative analysis between cases around questions such as “What made the implementation successful or unsuccessful?”, “What may explain the differences in implementation processes and outcomes?” (Anthony and Jack, 2009, Zucker, 2001). The case will consist of ICU staff (i.e., clinicians, managers / leaders) and those involved in implementing and delivering the FSI. Data collection will start at mid-intervention (around 9-12 months after first participant-in) and include focus group interviews with ICU staff, key informant individual interviews, documentation review, and observation of ICU team care delivery to families. New data sources might be used and included as necessary, which is in line with the adaptive design of case studies (Yin, 2018). Content analysis strategies (Erlingsson and Brysiewicz, 2017, Graneheim and Lundman, 2004) will be used to identify patterns within and across cases, building explanations for successful implementation, resulting in a logic model of contextual enablers and successful implementation strategies.

9.2 Assessment of Individual-Level Data

Individual participant-level data will be collected by local study coordinators after participant enrollment at admission (baseline), discharge, and 3, 6, and 12 months thereafter through psychometrically sound, family-reported outcome measures; that is, an online or paper-pencil survey. RedCap will be used as the electronic data capture (EDC) system. A personalized link to the online survey will be generated for each participant and assessment time-point, which will then be sent to study participants via email, SMS or other pre-determined means. If participants prefer to complete the outcome measures by paper and pencil, a paper version of the online survey will be sent to study participants with a stamped return envelope. Study coordinators will encourage participants to complete the outcome measures online, and participants will need to state their mode preference upon study enrollment.

9.2.1 Study Flow Table of Study Procedures and Assessments

Participant eligibility screening and enrollment will occur at the individual level using a consecutive sampling strategy. The participant timeline is displayed in Table 2.

9.2.2 Assessments of Demographic Information and Care Utilization from Family Members

At baseline, demographic attributes and prior care utilization of the family members will be collected. Family members will also complete a demographic and care utilization form at each time-point of data collection, and complete a brief form on patient status (see Table 7 for a detailed list of variables).

Table 7: Demographic, health status, work-related and care utilization information from family members

	Admission (Baseline)	Discharge (FU1)	3-12 months (FUs 2, 3, 4)
Demographics	Age, Gender, Civil status, Education Type of family member, Primary carer (yes / no), Co-habiting with patient (yes / no) or further persons, Frequency of contact Travel time to hospital	-	Change in civil status Primary carer (yes / no)
Health status	Self-perceived health (VAS) Prior/present psychiatric diagnosis (yes / no)	Self-perceived health (VAS)	Self-perceived health (VAS)
Care utilization	Prior / current psychological / psychiatric treatment (yes / no; if current, which kind, frequency of visits) Current care / treatment for a chronic condition (yes / no; if yes, which condition) Use of prescription drugs Previous ICU experience (as patient, as family of patient) Satisfaction with previous ICU / hospital experience as family of patient (VAS)	New / current psychological / psychiatric treatment (yes / no; if yes, which kind (if psychiatric inpatient treatment, LoS), related to critical illness (yes / no); if current, frequency of visits) Number of family physician visits / hospitalizations (if positive, related to critical illness (yes / no); if hospitalized, LOS) Use of prescription drugs	New / current psychological / psychiatric treatment (yes / no; if yes, which kind (if psychiatric inpatient treatment, LoS), related to critical illness (yes / no); if current, frequency of visits) Number of family physician visits / hospitalizations (if positive, related to critical illness (yes / no); if hospitalized, LOS) Use of prescription drugs
Work situation	Level of employment, income Sick leave / absence from work (yes / no; if yes: # of (half-)days, related to critical illness (yes / no))	Change in level of employment (if yes, related to critical illness (yes / no)), income Sick leave / absence from work (yes / no; if yes: # of (half-)days) Presenteeism	Change in level of employment (if yes, related to critical illness (yes / no)), income Sick leave / absence from work (yes / no; if yes: # of (half-)days) Presenteeism

9.2.3 Assessments of Routine Patient Data

At baseline and first follow-up, information on the patients' health condition and care utilization will be extracted from the clinical record. After that, family members will be asked to provide proxy information on patients' care utilization and functional status (see Table 8 for a detailed list of variables).

Table 8: Demographic, health status and care utilization information from patients

	Admission* (Baseline)	Discharge* (FU1)	3-12 months** (FUs 2, 3, 4)
Demographics	Age, Gender, Civil status	-	-
Health status	Medical diagnosis (MDSi) Mechanical ventilation (yes / no) Mechanical circulatory support (yes / no) SAPS-2[a], NEMS[b], SOFA[c] Trauma (yes / no); if yes, AIS[d]	Medical diagnosis (MDSi) Mechanical ventilation duration (days) Trachestomy Mechanical circulatory support (yes / no, days) NEMS[b], SOFA[c] Death (yes / no); if yes, date, cause, place, while (not) under full therapy (if not, reason) Organ donation (yes / no; if yes, which organ) with living will of patient / surrogate decision by family member	Death (yes / no); if yes, date, cause & place; if no, Functional status (Katz ADL / Lawton IADL)
Care utilization	Cause of admission Type of admission (expected, unexpected) Surgery (emergency, planned, none) Admitted from Previous ICU stays (yes / no) Prior need for informal / formal care (yes / no)**	Length of ICU stay Discharge destination Planned vs. unexpected transfer or discharge	Need for informal / formal care (yes / no); if yes, change, hours / frequency, more / less than before ICU treatment Family satisfaction with care onwards (VAS) (FU2)

*Extracted from clinical record, **reported by family member participant, [a]Simplified Acute Physiology Score, [b]Nine equivalents of nursing manpower use score, [c]Sequential Organ Failure Assessment Score, [d]Abbreviated Injury Scale

9.2.4 Intervention Documentation

For participants in the intervention arm, a structured intervention log will be completed by the interventionist. For each intervention contact, independent of the component, the following will be recorded: date, ICU or post-ICU day, duration in minutes, delivery mode (face-to-face, phone, online), number / type of family members and ICU staff participating, type of intervention component (encounter, therapeutic conversation, interprofessional family meeting), nurse intervention activity (relational engaging, family assessment, psycho-educational intervention, relationship-focused interventions, liaison & coordination, interprofessional communication, shared decision-making, making referrals), as well as referrals made to auxiliary services. Therein, any concomitant interventions exceeding usual care will also be registered. Usual care itself will not be documented.

9.2.5 Assessments of Family Member Outcomes

9.2.5.1 Assessment of Primary Outcome

Family satisfaction in ICU (FS-ICU-24R German version) is a well-established instrument (van den Broek et al., 2015, Wall et al., 2007), which has recently been updated to increase readability and extended with two questions (FS-ICU-24R). It assesses two factors: satisfaction with care (16 items) and satisfaction with involvement in decision-making (10 items). The response categories use a 5-point Likert scale (range 1-5), and each item is transformed to a standardized score of 0-100, whereby 100 indicates maximal satisfaction. Test-retest (10-day) reliability was

high in the original pilot r=.85 (Heyland et al., 2001), and the instrument has been shown to be sensitive to change in several intervention studies (van den Broek et al., 2015). The German version of the FS-ICU-24R demonstrates good internal consistency (Cronbach's alpha > .85), with no floor or ceiling effects (Harrison et al., 2015, Stricker et al., 2007). The FS-ICU-24R will be assessed at discharge from ICU.

9.2.5.2 Assessments of Secondary Outcomes

Questionnaire on the Quality of Physician-Patient Interaction (QQPPI original German version): The QQPPI is used to assess quality of communication between the ICU staff and family members during consultation. The 14 items assess aspects such as relationship-building, information exchange and shared decision-making, which are rated on 5-point Likert scale from 1 (I do not agree) to 5 (I fully agree). The mean score ranges from 1-5, with higher scores indicating higher quality. Psychometric properties of the original German version are solid, with Cronbach's alpha .95 and test-retest reliability .59 (Bieber et al., 2010). The QQPPI has been appraised as one of the most psychometrically sound measures of health professional-patient interaction (Zill et al., 2014).

Family Perceived Support Questionnaire (ICE-FPSQ German version): The ICE-FPSQ measures families' perception of support provided by nurses. It has two subscales – emotional support (9 items) and cognitive support (5 items) – which are rated on a 5-point Likert scale ranging from 1 (almost never) to 5 (all of the time). A sum score is calculated for the total scale (range 14-70) and each subscale – emotional support (range 9-45) and cognitive support (range 5-25) – with higher scores indicating perception of better family support by nurses. The Icelandic and Swedish versions have demonstrated high internal consistency, with Cronbach's alpha > .87 and satisfactory test-retest stability (Bruce et al., 2016, Sveinbjarnardottir et al., 2012). Since this instrument best operationalizes the nurse interventions' component of systemic family intervention, it will be translated and validated in German prior to its use in the trial, employing a systematic procedure (Sousa and Rojjanasrirat, 2011).

Family Assessment Device – General Functioning Scale (FAD-GF-12 German version): The FAD General Functioning scale is used to assess overall functioning of the family system (Beierlein et al., 2017, Epstein et al., 1983, Mansfield et al., 2015). Six positive and six negative items are rated on a 4-point Likert scale, ranging from 1 (strongly agree) to 4 (strongly disagree). After recoding the six negative items, an average score is calculated (range 1-4), with lower scores reflecting better functioning. Average GF scores over 2.0 indicate family dysfunction (Miller et al., 1985). The FAD-GF has good test-retest reliability (r=.60 after 12 weeks) among patients with PTSD, and both the FAD and FAD-GF have demonstrated responsiveness in intervention studies (Staccini et al., 2015). The German version of the FAD-GF scale demonstrates good internal consistency among adults in families with parental cancer (Cronbach's alpha=.87) (Beierlein et al., 2017).

Brief Resilience Scale (BRS German version): Conceived to measure the essence of resilience as the ability to bounce back from stress (Smith et al., 2008), BRS is made up of six items rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse coding the three negatively formulated items, the mean score can be calculated (range 1-5) from the sum (range 6-30) with higher scores indicating greater resilience. Evidence from intervention studies suggests the scale is sensitive to change (Bluth and Eisenlohr-Moul, 2017, Romcevich et al., 2018). The German version (Chmitorz et al., 2018, Kunzler et al., 2018) demonstrates good internal consistency (Cronbach's alpha .85). In this study, the items will be reformulated from "I" to "we" statements to assess family ability to bounce back from stress.

Distress Thermometer (DT German version): The Distress Thermometer is a validated screening instrument for distress originally (but still primarily) used among cancer patients (Donovan et al., 2014, Garrubba, 2019, Mehnert et al., 2006, Zwahlen et al., 2008, Zwahlen et al., 2011). Respondents are asked to rate how much distress they feel in the past week on a single vertical thermometer with two anchors defined as 0 (no distress) to 10 (extreme distress) along an 11-point Likert scale. A common cut-off of 4 indicates potential distress (Donovan et al., 2014, Ma et

al., 2014). It can detect changes over time (Gessler et al., 2008, Ohnhäuser et al., 2018, Thalén-Lindström et al., 2013). The German version – using the term “Belastung” as anchor – has been tested among both cancer patients (Mehnert et al., 2006) and their families (Zwahlen et al., 2008) against HADS with good results (AUC > .71). Even though the instrument has been used primarily among patients with cancer, it is a completely generic visual analog scale (VAS) (McCormack et al., 1988) comparable to those used to measure distress among minors (Benjamin et al., 2010) and perceived stress in healthy populations (Lesage et al., 2012).

Impact of Events Scale-6 (IES-6 German version): The IES-R - a widely used instrument to assess psychological distress in ICU family members (Alfheim et al., 2019, Kentish-Barnes et al., 2009) - measures the presence and severity of symptoms associated with a traumatic event during the past week. In the IES-R, 22 items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely) (Maercker and Schützwohl, 1998, Weiss and Marmar, 1996) and include three subscales: intrusion (7 items), avoidance (8 items), and hyperarousal (7 items). The 6-item brief version (IES-6) includes 2 items from each of the three subscales, and its simple sum score (0-24) has been shown to be highly correlated to the IES-R in various populations (Thoresen et al., 2010). It can detect changes over time as well as varying degrees of severity (Weiss & Marmar, 1996). The German version of the IES-R-6 (Maercker and Schützwohl, 1998, Thoresen et al., 2010, Weiss and Marmar, 1996) is a measure with acceptable to good internal consistency (Cronbach’s alpha of .80) and satisfactory test-retest reliability r=.66-.80.

Hospital Anxiety and Depression Scale (HADS German version): HADS is used widely in clinical practice and research, including studies among ICU family members (Davidson et al., 2012, Kentish-Barnes et al., 2009, McAdam and Puntillo, 2009). It is made up of 14 items with different response categories rated on a 4-point Likert scale from 0 to 3, and is scored in two subscales – anxiety (HADS-A, 7 items, range 0-21) and depression (HADS-D, 7 items, range 0-21) – with higher scores indicating worse symptoms. A score between 8-10 is indicative of mild depression or anxiety and 11-21 of caseness for depression or anxiety (Davidson et al., 2012, Kentish-Barnes et al., 2009, McAdam and Puntillo, 2009). The scale can detect changes over time (Angst et al., 2008, Herrmann, 1997) as well as varying degrees of severity (Herrmann, 1997). The German version demonstrates good internal consistency (Cronbach’s alpha > .80 for both subscales) and high test-retest reliability – .81 for HADS-A and .89 for HADS-D – after 1 week (Herrmann-Lingen C. et al., 2011).

WHO-5 Well-being Index (WHO-5 German version): WHO-5 was developed to measure subjective psychological well-being (Bech et al., 2003). Widely used in European surveys (Eurofound, 2017, Winther Topp et al., 2015), it is made up of five items tapping three major dimensions of positive affect as well as energy within the past 2 weeks rated on a 6-point Likert scale from 0 (at no time) to 5 (all of the time). The sum of the raw scores (0-25) is multiplied by 4 to yield a range from 0-100, whereby higher scores indicate greater well-being. A cut-off of ≤50 is indicative of depression (Winther Topp et al., 2015). The scale can detect response to treatment, whereby a 10-point change is considered clinically relevant (Winther Topp et al., 2015). The German version (Brähler et al., 2007) demonstrates high internal consistency (Cronbach’s alpha .92).

General Quality of Life (QoL-VAS): An adapted version of a Visual Analog Scale (VAS) as used in the EuroQol EQ-5D questionnaire (Rabin and de Charro, 2001) will be employed to measure general quality of life. Participants are asked to rate their self-perceived general quality of life from 0 (lowest quality) to 100 (highest quality). Referring to general quality of life, rather than health-related quality of life, the scale implements anchors to foster comparability across individuals (as discussed, for example, by Drummond et al. (2015) and Torrance et al. (2002)).

Satisfaction with Life Scale (SWLS-5 German version): Developed to measure the global dimension of subjective well-being (Diener et al., 1985), SWLS is made up of five items rated on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). The sum of the scores (range 5-35) can be treated as a continuous or ordinal variable along the following thresholds: 5-9 extremely dissatisfied, 10-14 dissatisfied, 15-19 slightly dissatisfied, 20 neutral, 21-25 slightly satisfied, 26-30 satisfied, 31-35 extremely satisfied. The scale can detect changes over time as

well as response to treatment (Pavot and Diener, 2008). The German version (Schumacher, 2003) demonstrates high internal consistency (Cronbach's alpha .89-.92) (Glaesmer et al., 2011, Hinz et al., 2018).

9.2.5.3 Assessment of Safety Outcomes

Not applicable.

9.2.5.4 Assessment in Participants who Prematurely Stop the Study

If participants withdraw before their end-of-study assessment timepoint, the reason for withdrawal will be recorded and – if the participant agrees – the data on the clinical status of the patient will be collected (change in health status or death, timepoint of death). No follow-up is planned.

9.2.6 Procedures at Each Visit / Assessment Timepoint

9.2.6.1 *Screening*

Patients admitted to study ICUs will be consecutively screened for study eligibility within 48 hours by the local principal investigator or his / her delegates, that is, a team of designated clinicians. Screening will occur once per day during the week, and at least every second day over the weekend. If the patient-related inclusion criteria are met, the patient's family members who meet the inclusion criteria are identified next. As only one family member per patient can be enrolled in the study, the local principal investigator or his / her delegates need to determine, together with the patient or the patient's family, who will be the family member most affected and involved in the patient's critical illness situation, and will be – given his or her informed consent – invited and enrolled into the study.

9.2.6.2 *Enrollment*

The eligible family member(s) will be informed about the study purpose and procedures either by the local principal investigator, his / her clinical delegates, or the study coordinator within the first 72 hour after the patient's ICU admission. They will receive the study flyer (which will also be displayed in waiting areas and be included in ICU information brochure) and study information. Potential participants will have the opportunity to ask questions. If the eligible family member agrees to participation, s/he will be enrolled into the study after they received the necessary time to make a decision, either by the local principal investigator, his / her clinical delegates, or the study coordinator. Enrollment needs to occur within 96 hours of patient admission to ICU.

9.2.6.3 *Baseline Assessment (ICU Admission - T0)*

The baseline assessment will occur within the first 96 hours after patient admission, and after the necessary informed consent forms have been signed.

It will consist of a self-administered questionnaire (i.e. specifically generated, individual link or QR code that can be used to assess the online questionnaire, or paper-pencil questionnaire if participants wish to answer the question in paper format) that includes:

- a demographic form
- a form assessing prior care utilization and work situation
- family-reported outcome measures (FAD-GF-12, BRS-6, distress thermometer, HADS-14, IES-6, SWLS-5, WHO-5, QoL-VAS).

The online questionnaire will be either sent by SMS or Email or opened for family members to complete on a mobile device (i.e. ipad). Paper-pencil questionnaires will be handed to participants in persons or mailed to their home address with a stamped and addresses envelope. Family members will be able to complete the questionnaire at a place of their choice. Completion will require about 30-45 minutes. Patient data (as described in Table 8 in section 9.2.3) will be

extracted from the clinical record and inserted into the eCRF. Participants will be informed about the next assessment time point, which will be at or following patient discharge from ICU (incl. transfer or death).

9.2.6.4 First Follow-up (FU) Assessment (ICU Discharge – T1)

The first follow-up assessment will occur at or after patient discharge from ICU (-24 hours to +14 days). It will consist of a self-administered questionnaire (i.e. specifically generated, individual link or QR code that can be used to assess the online questionnaire, or paper-pencil questionnaire if participants wish to answer the question in paper format) that includes:

- a demographic form
- a form assessing care utilization and work situation
- family-reported outcome measures, including the primary outcome (FS-ICU-R-24, QQPPI-14, ICE-FPSW-14, FAD-GF-12, BRS-6, distress thermometer, HADs-14, IES-6, SWLS-5, WHO-5, QoL-VAS).

The online questionnaire will be either sent by SMS or Email or opened for family members to complete on a mobile device (i.e. iPad). Paper-pencil Questionnaires will be handed to participants in persons or mailed to their home address with a stamped and addresses envelope. Family members will be able to complete the questionnaire at a place of their choice. Completion will require about 45-60 minutes. Patient data will be extracted from the clinical record and inserted into the eCRF. Participants will be informed about the next assessment timepoint, and a date will be set.

9.2.6.5 *Second to Fourth Follow-up (FU) Assessments (3 months after ICU discharge - T2, 6 months - T3, 12 months - T4 after ICU Discharge)*

The second (end of treatment), third and fourth (end of study) assessment timepoints (± 14 days), will consist of a self-administered questionnaire (i.e. specifically generated, individual link or QR code that can be used to assess the online questionnaire, or paper-pencil questionnaire if participants wish to answer the question in paper format) that includes:

- a demographic form
- a form assessing care utilization and work situation
- family-reported outcome measures (FAD-GF-12, BRS-6, distress thermometer, HADs-14, IES-6, SWLS-5, WHO-5, QoL-VAS).
- a form assessing patient-related data via family members (i.e. care utilization and health / functional status) will be assessed via a structured format and the Katz Scale for Activities of Daily Living and the Lawton Scale for Instrumental Activities of Daily Living)

The online questionnaire will be either sent by SMS or Email. Paper-pencil Questionnaires will be mailed to their home address with a stamped and addresses envelope. Participants will be informed about the next assessment timepoint, and a date will be set. They will be able to complete the questionnaire at a place of their choice. Completion will require about 30 - 45 minutes.

9.2.6.6 *End of Study Assessment*

The End of Study Assessment is equal to the fourth follow-up assessment described in section 9.2.6.5.

10 SAFETY

The Sponsor’s SOPs provide more detail on safety reporting.

No serious adverse events (SAEs) are expected to be causally related to the study intervention. Nevertheless, during the entire duration of the study, any serious adverse events affecting the participants (family members) are collected and documented in source documents. Reportable events are recorded in the electronic case report form (eCRF). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including the follow-up intervention after discharge of the patient.

10.1 Definitions

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation participant after the intervention and which does not necessarily have a causal relationship with this intervention. An AE can therefore be any unfavorable and unintended finding, symptom, or disease temporally associated with the intervention, whether or not related to the intervention. An AE may also consist of a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event

A serious adverse event is defined as any event which:

- requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
- results in permanent or significant incapacity or disability;
- is life-threatening or results in death; or
- causes a congenital anomaly or birth defect.

10.2 Recording and Assessment of Serious Adverse Events

The investigator has the responsibility for SAE identification, documentation, and assessing the causal relationship with the study intervention (although no relationship is expected).

All SAEs will be fully documented in the appropriate eCRF. For each SAE, the investigator will provide the onset, duration, treatment required, and outcome.

The assessment by the investigator regarding the study intervention relation is done according to the following definitions:

Unrelated	• The event started in no temporal relationship to the family intervention applied and • The event can be definitely explained by underlying diseases or other situations.
Related	• The event started in a plausible temporal relationship to the family intervention applied and • The event cannot be definitely explained by underlying diseases or other situations.

10.3 Reporting of Serious Adverse Events

If in the course of the clinical trial serious adverse events lead to the death of a participant in Switzerland, the investigator must report this:

- to the Sponsor **within 24 hours** after they become known;
- and to the competent ethics committee (CEC) **within 7 days**.

Safety and protective measures

If immediate safety and protective measures regarding the participants (family members) have to be taken during the conduct of this clinical trial, the investigator must notify the CEC of these measures, and of the circumstances necessitating them, **within 7 days**.

Annual Safety Report

All SAEs will be summed up in the **annual safety report (ASR)** and submitted to the CEC. The ASR shall contain:

- A summary of all SAEs including the severity and the causal relationship to the intervention as well as information on the safety of participants.
- The accompanying letter provided with the ASR should contain a short summary of the status of the clinical trial in Switzerland (number of centers open/closed, number of patients recruited/recruitment closed, and number of SAEs).

10.4 Follow up Information on Serious Adverse Events

No follow-up information on SAEs is planned.

11 STATISTICAL METHODS

11.1 Hypothesis

Null Hypothesis (H_0): Family satisfaction with the ICU, as measured by the FS-ICU-24R total score at discharge from ICU (T1), does not differ between the intervention group and the control group. The intervention effect, β, is zero: $\beta = 0$.

Alternative Hypothesis (H_A, two-sided): Family satisfaction with the ICU, as measured by the FS-ICU-24R total score at discharge from ICU (T1), differs between the intervention group and the control group. The intervention effect, β, is non-zero: $\beta \neq 0$.

Our actual research hypothesis is one-sided (superiority of intervention vs. control), but the effect of the intervention vs. the control will be estimated with a two-sided 95 % confidence interval, corresponding to a two-sided significance level of 5 %.

11.2 Determination of Sample Size

Assuming a difference in FS-ICU-24R total score between the intervention and control groups of 5.5 and a within-group standard deviation of the FS-ICU-2R4 total score of 16.3, as observed in a previous study by our group (Naef et al., 2021), we would need a total of 278 subjects in a standard RCT (with n_{RCT}=139 per arm) with 1:1 randomization to have a power of 0.8 at a significance level of 0.05. However, due to the design effect (Kerry and Bland, 1998), which depends on the average cluster size and on the intra-cluster correlation coefficient (ICC), the number of participants required for our cluster-randomized trial is bigger than the sample size of a standard RCT. We assumed an ICC of 0.03 and a coefficient of variation in cluster size of 0.2.

Since the number of clusters is more limiting for this study than cluster size, we used the approach described by (Hemming et al., 2017) to derive the minimum number of clusters required for each condition to detect the desired effect size at the desired power, and rough estimates of cluster size for when the number of clusters is increased. Assuming unlimited cluster size, the minimum number is simply n_{RCT} x ICC = 5 clusters. Increasing the number of clusters per condition to 6, 7 or 8 (one, two or three more than the minimum), the cluster size could be reduced to n_{RCT}=139, $\frac{n_{RCT}}{2}$=70, and $\frac{n_{RCT}}{3}$=47, respectively.

We then conducted a series of precise power calculations, using the R packages *clusterPower* (Kleinman et al., 2017) and *sse* (Fabbro, 2019). The difference in FS-ICU-24R total score between groups was fixed at 5.5, the variance within groups at 16.3^2=265.69, and the significance level at 0.05. A range of clusters per condition $n_{i=1,\ldots,18}$=3,…,20 was considered, together with a range of mean cluster sizes of 10-300 and a range of intra-cluster correlation coefficients of 0.01-0.1. With an average cluster size of 50 evaluable patients and an ICC of 0.03, 8 clusters need to be randomized to each condition to achieve a power of 0.8. To account for a drop-out rate of 10 % of patients within clusters (but not dropouts of entire clusters), an average number of 56 patients should be recruited per cluster.

11.3 Planned Analyses

The detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Department of Biostatistics, University of Zurich. All analyses will be performed in the R system for statistical computing and graphics (R Core Team, 2020).

11.3.1 Datasets to be Analyzed, Analysis Populations

Our analysis will include all study participants recruited in all participating clusters. We will adhere to the intention-to-treat principle at cluster-level and participant-level as much as possible. Clusters and their participants will be analyzed given the condition to which they were assigned. Should a patient be transferred to another cluster (other ICU), the family will be analyzed in the original cluster.

11.3.2 Primary Analysis

The primary outcome, FS-ICU-24R total score (at T1), will be analyzed by a linear mixed-effects model with a random intercept per cluster to account for the non-independence of patients (and their family members) from the same cluster. Due to the small number of clusters, the model will include the treatment (intervention vs. control) as the only explanatory variable (main analysis). To adjust for the small number of clusters, we will use the Satterthwaite approximation for the denominator degrees of freedom, as recommended by (Leyrat et al., 2018). The ICC will be estimated from this model (and reported) using the estimates of residual variance and between cluster variance.

The following *sensitivity analyses* are planned for the primary outcome (and may also be applied to the secondary outcomes):

- To gain precision and to adjust the treatment effect estimate for potential confounding, we will conduct several covariate-adjusted analyses regarding cluster-level covariates and/or participant-level covariates.
    - Since the number of clusters limits the number of cluster-level covariates to adjust for, we will only add one of the following cluster-level covariates at a time to the model: the specialization of the ICU (specialized vs. general ICU, as used in the minimization procedure), overall ICU staffing, and the quality-of-care indicator. The center, also used in the minimization, will not be included as a covariate, because

most ICUs are in a different center (and few ICUs from the same center will participate).

    - Participant-level covariates will be added to the model together. These include the patient's age, the cause of admission, the SAPS-2 score of the patient (mortality risk), as well as the family member's previous ICU experience. These participant-level covariates will be added to the main model described above and potentially to one or several of the cluster-level covariate adjusted models described above.

- To assess the sensitivity of the results with regard to missing outcome measurements, we will apply the main model described above (and potentially one or several of the covariate adjusted models) to a multiply imputed data set.
- Differences between the main analysis and the sensitivity analyses will be described and discussed.

11.3.3 Secondary Analyses

The secondary outcomes regarding quality of care, which are only measured once at the end of the ICU stay (T1), will be analyzed with the same type of model as described above for the primary outcome. All other secondary outcomes, which are measured at baseline (T0) and four times after the start of the intervention (T1-T4), will be analyzed by a linear mixed-effects model with a random intercept per cluster and a random intercept per family member (nested within cluster) to additionally account for the non-independence of repeated measurements from the same study participant. The serial autocorrelation of residuals will be modelled using a first order autoregressive correlation structure. The models will include the treatment (intervention vs. control), the corresponding baseline measurement of the outcome analyzed, the visit and the visit × treatment interaction to assess whether the treatment effect changes over time.

Subgroup analyses are planned for the following baseline characteristics regarding the primary outcome:

1. Cluster characteristics:
    - specialization (specialized vs. general ICU)
    - overall ICU staffing
    - quality of care indicator (sum score)
2. Patient or family member characteristics:
    - patient's age
    - patient's gender
    - patient's cause of admission (expected vs. unexpected)
    - patient's mortality risk, as assessed by SAPS-2 score upon admission
    - type of relationship between patient and family member
    - family member's prior ICU experience
    - family resilience, as assessed by the Brief Resilience Scale (BRS)
    - family functioning, as assessed by the Family Assessment Device – General Functioning Scale (FAD-GF-12)
    - family member's Hospital Anxiety and Depression Scale (HADS)

For each subgroup variable, a linear mixed-effects model will be fitted for the primary outcome, as described above (section 11.3.2). The subgroup variable and the interaction between the subgroup variable and the treatment will be added as explanatory variables. A significant interaction between one of the subgroup variables and the treatment would indicate a different treatment effect in the corresponding subgroups, or along a gradient, for the continuous subgroup variables.

Further, patient survival status and ICU length of stay are two participant-level covariates that are of interest but are measured during the ICU stay (during or after the intervention) and therefore do not qualify as baseline characteristics to adjust for in these models. However, for exploratory purposes, we will nevertheless fit a model including the treatment together with patient survival status, length of ICU stay, and the three two-way interactions, which will need very cautious interpretation. Similarly, we will fit a model including the intervention dose (zero for the control group).

In addition, we will compute Cronbach's alpha for total scores and subscales of all family-reported outcome measures used in our study.

Furthermore, the working hours per intervention (FSI) spent by the family nurses will be analyzed in an economic comparison with the mental health of the family members (psychological distress according to the secondary outcome measures, see Table 3) and their volume of work (level of employment, absence from work, see Table 7).

11.3.4 Interim Analyses

None.

11.3.5 Safety Analysis

Not applicable.

11.3.6 Deviation(s) from the Original Statistical Plan

If substantial deviations of the analyses as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analyses from the protocol or from the detailed statistical analysis plan will be listed and justified in a separate section of the final statistical report.

11.4 Handling of Missing Data and Drop-Outs

We will analyze complete cases in the main analysis and use multilevel multiple imputation of missing outcome data at the participant level (van Buuren, 2018, chapter 7) in a sensitivity analysis (section 11.3.2). We do not expect any clusters to be missing as a whole, but would exclude them from the analysis if present.

12 ELIGIBILITY OF THE PROJECT SITE(S)

This trial is restricted to ICUs from the German-speaking part of Switzerland operating as regional or specialist centers and have been certified by the Swiss Society for Intensive Medicine. Further requirements are described in section 7.1.1..

13 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor implements and maintains quality assurance and quality control systems with written SOPs and Working Instructions (WIs) to ensure that trials are conducted, and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor is responsible to have written SOPs and WIs in place for the study and to provide them to all participating study sites. The Principal Investigators at all sites must have a manual of the relevant SOPs and WIs for the study on site and are responsible for proper training of all involved study personnel for the respective procedures.

Monitoring and audits will be conducted during the course of the study for quality assurance purposes.

13.1 Data Handling and Record Keeping

The study will strictly follow the protocol. If any changes become necessary, they must be laid down in an amendment to the protocol (ref. 2.9).

13.1.1 Cluster-Level Case Report Forms

For data management and monitoring at the cluster level, a paper Case Report Form (pCRF) will be used. Clusters will fill in the pCRF, which will serve as the source document. All requested information in the pCRF should be completed in a neat, legible manner. Use of a black ball pen is recommended to ensure clarity of reproduced copies in the pCRF. All corrections in a pCRF must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed by the investigator. Data that are not available or not done should be made clear by adding NA or ND. A declaration ensuring accuracy of data recorded in the case report forms must be signed by the investigator.

The original pCRFs and the necessary data extracted from the Minimal Data Set (MDSi; as an Excel sheet) will be sent to the Sponsor, while the clusters store a copy of the original pCRFs. The Sponsor will then enter the pCRF into an Excel sheet. After each step of entering the pCRF data into Excel, a new version of the respective Excel file will be stored, a PDF file will be generated, and the team member who edited the file will be registered.

The accuracy of the digital data representing the hand-written pCRFs will be tested by random sampling of 10% of the clusters (i.e., two clusters) per section of the pCRF to which the four-eyes principle will be applied. A second member of the research team, who will not have been previously involved in entering the pCRF data into Excel, will compare the digital data with the hand-written originals for errors. In case the error rate should exceed 1%, the according section of the pCRF will be re-entered into Excel for all clusters by a different team member, and the resulting digital data will be assessed for accuracy again as described above. If the error rate should exceed 5%, the entire pCRFs of all clusters will be re-entered and testing for accuracy will start anew.

All Excel files that have been completed and successfully checked for correctness are blocked for further changes and a final PDF version is saved. The Sponsor will store all digital data on secure servers of the University of Zurich. Individual user access control will be strictly limited to the members of the study team at the University of Zurich. Any cluster files and source data must be archived for the at least 10 years according to the feasibility of the investigational site, e.g., hospital, institution, or private practice.

13.1.2 Participant-Level Case Report Forms

All participants who either entered the study or were considered non-eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log.

For data and query management, monitoring, reporting, and coding at the individual participant level, electronic, and if participants prefer, paper case report forms (eCRF/pCRF), one for each

enrolled study participant, are to be filled in with all relevant data pertaining to the participant during the study.

An internet-based secure data base, the electronic data capture (EDC) software REDCap (www.project-redcap.org) will be used for all aspects of data processing and management at the individual participant level. REDCap was developed by an informatics core at Vanderbilt University in 2004, with ongoing support from US National Center for Research Resources (NCRR) and US National Institute of Health (NIH), grants NIH/NCATS UL1 TR000445. REDCap was specifically developed around HIPAA security guidelines, is GCP-compliant, and fulfils the Swiss regulatory requirements regarding the collection of patient data in clinical trials or non-interventional studies and patient registries and the Swiss/EU data protections laws. Ongoing maintenance and use of this software is contractually agreed upon between the study Sponsor and the Data Management Department of the CTC Zurich.

The eCRFs are generated via a study-specific data dictionary defined in an iterative self-documenting process by members of the research team with planning support from the Data Management Department of the Clinical Trials Center, University Hospital Zurich, Switzerland (CTC Zurich).

If participants prefer or are unable to complete the eCRF, they will complete the equivalent pCRF. Study coordinators will then enter the pCRF into the eCRF. All requested information in the pCRF should be completed in a neat, legible manner. Use of a black ball pen is recommended to ensure clarity of reproduced copies in the CRF. All corrections in a pCRF must be made in a way that does not obscure the original entry. Previously selected, but ultimately unselected, checkboxes must be fully colored and text responses must only be crossed out with a single straight line. The correct data must be inserted, dated, and initialed by the investigator. Data that are not available or not done should be made clear by adding NA or ND. A declaration ensuring accuracy of data recorded in the case report forms must be signed by the investigator.

Data variables will be entered into the secure REDCap database along the ALCOA+ data integrity principles originally introduced by the US Food and Drug Administration (FDA), thereby ensuring collection and transfer of data in an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available manner.

Each study center will assign the role of Data Entry to at least one study representative with adequate qualifications for the use of EDC software.

eCRFs/pCRFs must be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the eCRF/pCRF by name. Appropriate coded identification (e.g., participant number) must be used. Initials must not be used in combination with the date of birth in the eCRF/pCRF for identification of the study participant. The investigators assure to perform a complete and accurate documentation of the participant data in the eCRF.

All data entered into the eCRF (such as paper-pencil participant questionnaires - pCRF, intervention logs, if applicable), with exception of the online questionnaires completed directly by participants via the survey function of REDCap (eCRF), must also be available in the individual participant file either as printouts, as notes taken by either the investigator or another responsible person assigned by the investigator. Patient-related data will be available in the electronic clinical patient records.

Essential documents must be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45). Any participant files and source data must be archived for the longest possible period of time according to the feasibility of the investigational site, e.g., hospital, institution, or private practice.

13.1.3 Specification of Source Documents

The following documents are considered source data, including but not limited to:

At the cluster level:

- ICU-specific assessment forms of quality of family care and degree of family engagement
- ICU-characteristics (SGI minimal data set)
- Implementation activity and cost logs (only intervention arm)

At the individual participant level:

- individual participant information
- SAE worksheets
- Clinical patient records
- Nurse/physician records
- Records of interventionists (i.e. structured intervention log, only intervention arm)
- Records of study coordinators
- Electronic data capture system (REDCap) – survey-enabled eCRF part that is directly completed by participants
- Paper CRF forms that are directly completed by participants due to their preference over the eCRF

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study.

The following information (at least but not limited to) should be included in the source documents at the individual participant level:

- Inclusion and exclusion criteria details
- Participation in study and signed and dated Informed Consent Forms
- Patient-related information
    - Demographics
    - Clinical data (patient records at T0 and T1, family-reported patient data from T2-T4)
    - Care utilization data (patient records at T0 and T1, family-reported patient data from T2-T4)
- Family-related information
    - Demographic, family relationship information, and employment-related information)
    - Health-related data
    - Care utilization data
    - Family-reported outcome measures
    - Intervention documentation (only intervention arm)
- Assessment timepoint dates
- SAEs affecting the participants (family members)
- Reason for premature discontinuation

13.1.4 Record Keeping / Archiving

The server hosting the REDCap EDC system and the study MySQL database is managed by the CTC Zurich in close collaboration with the ICT department of the University Hospital of Zurich. A multi-level back-up system is in place. Whole system internal back-ups including the database are run several times per day and an additional external back-up onto tape once a day. The back-up tapes are stored in a secure place in a separate building on the premises of the University Hospital of Zurich. A copy of the study database will be stored securely by CTC Zürich for at least 10 years. The Sponsor further maintains essential documents and source data in the Trial Master File and archives interim and final reports in electronic and hard copy format for at least 10 years.

13.2 Data Management

The trial manager and study coordinators will receive training by the Clinical Trial Center at the University Hospital Zurich / University of Zurich (CTC Zurich) with regards to maintaining quality assurance and study documentation and conducting basic source data verification (on site and / or online). Furthermore, the trial manager and study coordinators at each study center will attend documented and standardized elementary training on the use and application of the EDC software system REDCap conducted by the CTC data management team in order to facilitate database management and eCRF completion and oversight. The trial manager will support study coordinators in the study centers.

The REDCap system operation is compatible with Linux, UNIX, Windows, or Mac interfaces and requires a SMTP e-mail server, which is accessed via PHP web-based Front End (e.g., Microsoft IIS or Apache). Study data is stored on a MySQL database server, hosted by the CTC Zurich, which holds a RedCap End-User License Agreement for this EDC system.

Data access and security are governed by the user and access management system of the EDC software REDCap and the standard high-level local ICT security settings employed at the CTC Zurich. A role-based user concept with personal login regulates permission for each user (e.g., for site investigator, monitor, administrator, etc.) to access the system and database. Role- and user-based access control will regulate individual user rights for data entry, review, export, and reports. Data Access Groups will be generated to segregate users according to their study center affiliation. This is especially useful for multi-centric studies where the data entered by one institution should not be accessible or viewable by others within the same project. A current list with signatures and names of all authorized study personnel with access to the study records will be filed in the study site and trial master file, respectively. A built-in data logging tool (audit trail) ensures that any changes to the project or user activity (date and time stamp and user log), including contextual information (e.g., the project record being accessed) are continuously tracked in real-time and accessible online or via downloadable audit table.

According to local legislation in Switzerland, the Federal Act on Data Protection of June 19, 1992 (DPA) together with its ordinances, the Ordinance to the Federal Act on Data Protection (DPO) and the Ordinance on Data Protection Certification (ODPC) govern issues of data protection and privacy matters. Whilst the Sponsor will adhere to local legislation, the principles of good practice regarding processing of personal data in clinical research shall apply. Therefore, data handling will generally involve:

- Fair and lawful data processing
- Processing which is in line with the original and specified purpose
- Collection of data which is adequate, relevant and not excessive
- Collection of data which is accurate and kept up to date (where relevant)
- Kept no longer than it is necessary for the intended purpose
- Processed in line with the rights of individuals
- Kept secure with appropriate technological and organizational measures

In line with this, data will not be transferred unless there is adequate protection and regulation around the data being shared.

13.3 Routine Monitoring

Monitoring visits at the Sponsor site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time. The Sponsor organizes professional independent monitoring for the study.

All original data including all participant files and progress notes must be available for monitoring. The monitor will review all or a part of the eCRF/pCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. The Sponsor site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure monitoring. According to the CTC's Monitoring SOP the extent and nature of monitoring activities based on the objective and design of the study will be defined in a study specific Monitoring Plan.

Data monitoring will be initiated after inclusion of 10 study participants at each study center, with a focus on the participants' eligibility, documentation of the intervention at the corresponding study centers and completion of questionnaires by the participants. Monitoring will be conducted by the CTC Zurich and partially by a sponsor-delegated internal person. Observations and findings will be documented by the responsible Clinical Research Associates (CRAs) of the CTC Zurich or the sponsor-delegated person and made available to the trial manager and/or local study site for feedback and support. Patient eligibility will then be reviewed for an additional 20 - 50% of study participants. Random clinical data monitoring will also be undertaken by the CRAs of the CTC Zurich in four study centers, where up to 10% of the enrolled patients will be source-data verified.

As the study endpoints rely mainly on the completion of questionnaires by the participants, system-supported automatic notifications on the eCRF completion status will be implemented to ensure data completeness. For pCRFs directly filled in by participants, study coordinators will check their completeness and, if necessary, obtain missing data directly from participants via phone. Programmable data quality rules will allow spot checks on rates of completion, identification of missing data and follow-up measures on identifiable deviations from protocol. Electronic and central data validation is supported by means of automated and programmable data checks tracking plausibility (range and date/time checks). Central data validity checks against pre-determined parameters are run either automatically or ad hoc, to detect inconsistencies and identify missing data for source data verification. Further data quality assurance is provided by implementing study-specific reports.

13.4 Audits and Inspections

A quality assurance audit/inspection of the study intervention will be conducted by the Sponsor site. The quality assurance auditor / inspector will have access to all medical / nursing records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data / documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

The Sponsor will conduct audits at the study centers of the intervention arm regarding intervention documentation and intervention delivery (see section 8.3).

13.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits, and inspections.

13.6 Storage of Health Data

Quantitative health-related data will be collected prospectively over a period of 18 months (or until the sample size is reached). A single electronic dataset will be generated by combining data of 4 data types from a sample size of 16 clusters with 56 participants each, resulting in 896 family

members (corresponding to 896 ICU patients), randomized to either receive standard care or treatment intervention (FSI).

Information captured for the outlined pCRF will be entered into secure and access-restricted electronic case report forms (eCRFs). Data captured through means of paper questionnaires (where applicable) and/or cluster-level data originally collected on paper will serve as source data to be kept securely on site as described by the study protocol and local study site standard operating procedures (SOPs) and/or working instructions (WIs). Electronic transfers of qualitative data used for further analyses, where applicable, will be kept securely on study-specific and access-restricted files under the Sponsor's supervision and control.

14 PUBLICATION AND DISSEMINATION POLICY

14.1 Dissemination of Study Results

After the statistical analysis of this trial, the Sponsor will make every endeavor to publish the data in a medical or nursing science journal. Emphasis will be placed on making scientific output as widely available as possible in order to encourage knowledge transfer and either secondary and/or meta-analyses as well as general reproduction efforts. All study centers and study participants will be provided with a lay summary of the study outcome (upon interest), and preliminary findings from both the outcome-based study evaluation as well as the case study will be shared by means of poster presentations, scientific talks and lay and scientific publications on a national (and international) level at appropriate platform events typically attended by ICU staff and health care professionals.

14.2 Reproducibility

An overview of the study protocol will be made accessible via the ClinGov trial registration database for researchers and the public. The study protocol will be published before recruitment launch. While the publication of clinical trial results is an ethical obligation under paragraph 30 of the Declaration of Helsinki (World Medical Association, 2013), the nature of clinical research datasets, as is the case in the present study, requires careful and considerate data access management throughout the data life cycle, including but not limited to its availability via open research data channels. General limitations of data sharing are typically governed by participant confidentiality issues, compliance with informed consent agreements and the protection of IP rights.

Outcome-related raw data will be securely managed but corresponding metadata will be made available at the earliest opportunity via appropriate data repositories so that the study data sets can be identified and found according to the FAIR data principles. To gain access to raw data, interested researchers will need to complete a data request form stating their affiliations and research objectives in connection with the dataset. This will allow a governing body (yet to be defined) to assess whether the researchers in question meet access criteria yet to be defined and whether research objectives are in line with the Sponsor's and the SNSF funding policies and regulations. Any subsequent data sharing will be subject to sign-off by the Sponsor's organizational Chief Information Security Officer (CISO) and relevant Data Sharing Agreements (to be handled by UNITECTRA) being drawn up and the respective ethical considerations and/or data protections laws being adhered to. No biological samples will be collected in this study.

15 FUNDING AND SUPPORT

15.1 Funding

The study is funded by the Swiss National Science Fund through the Investigator-Initiated Clinical Trial 2020 funding scheme (Beitrag Nr.: 33IC30_198778 / 1).

15.2 Other Support

The study is supported by the Swiss Society for Intensive Medicine, who recommends participation. The Society does not fund the study.

16 INSURANCE

Insurance is covered by “Versicherung für klinische Versuche und nichtklinische Versuche“ by Zürich Versicherungs-Gesellschaft AG (Policy no.: 14.970.888).

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate is filed in the Investigator’s Site File at each study center / cluster.

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18 APPENDICES

The following appendices are provided as separate documents attached to this study protocol:

Appendix A: Study Information and Informed Consent Forms / Study Flyers

Appendix B: Case Report Forms (CRFs)

Appendix C: Monitoring Plan