




BMJ Open Swiss Frailty Network and Repository: protocol of a Swiss Personalized Health Network's driver project observational study

Michael Gagesch ^{1,2}, Karin Edler,³ Patricia O Chocano-Bedoya,^{2,4} Lauren A Abderhalden,² Laurence Seematter-Bagnoud,^{5,6} Tobias Meyer,⁷ Dominic Bertschi,⁸ Dina Zekry,⁹ Christophe J Büla ⁶, Gabriel Gold,¹⁰ Reto W Kressig,^{7,11} Andreas E Stuck,⁸ Heike A Bischoff-Ferrari ^{1,2}

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For numbered affiliations see end of article.

Correspondence to

Dr Michael Gagesch;
michael.gagesch@usz.ch

ABSTRACT

Introduction Early identification of frailty by clinical instruments or accumulation of deficit indexes can contribute to improve healthcare for older adults, including the prevention of negative outcomes in acute care. However, conflicting evidence exists on how to best capture frailty in this setting. Simultaneously, the increasing utilisation of electronic health records (EHRs) opens up new possibilities for research and patient care, including frailty.

Methods and analysis The Swiss Frailty Network and Repository (SFNR) primarily aims to develop an electronic Frailty Index (eFI) from routinely available EHR data in order to investigate its predictive value against length of stay and in-hospital mortality as two important clinical outcomes in a study sample of 1000–1500 hospital patients aged 65 years and older. In addition, we will examine the correlation between the eFI and a test-based clinical Frailty Instrument to compare both concepts in Swiss older adults in acute care settings. As a Swiss Personalized Health Network (SPHN) driver project, our study will report on the characteristics and usability of the first nationwide eFI in Switzerland connecting all five Swiss University Hospitals' Geriatric Departments with a representative sample of patients aged 65 years and older admitted to acute care.

Ethics and dissemination The study protocol was approved by the competent ethics committee of the Canton of Zurich (BASEC-ID 2019-00445). All acquired data will be handled according to SPHN's ethical framework for responsible data processing in personalised health research. Analyses will be performed within the secure BioMedIT environment, a national infrastructure to enable secure biomedical data processing, an integral part of SPHN.

Trial registration number NCT04516642.

INTRODUCTION

With the ongoing demographical transformation, ageing societies convey an important challenge to present healthcare systems due to the growing number of older adults living

Strengths and limitations of this study

- This large multicentre study, recruiting 1000–1500 individuals will establish a new harmonised electronic Frailty Index (eFI) from routinely collected electronic patient data at all five Swiss academic geriatric centres.
- The new eFI has the potential to predict two very important adverse outcomes in acute care, length of stay and in-hospital mortality.
- Furthermore, these new data will be used to investigate the correlation between the eFI and a standardised clinical Frailty Instrument.
- Our study is not intended to establish long-term outcomes in participants identified as frail versus their robust counterparts.
- No report on potential interventions for participants identified as frail or at-risk of becoming frail is included at this stage of the project, however we aim to lay groundwork for a future implementation of frailty screening in clinical care.

with accumulating deficits, multimorbidity and frailty.¹ At the same time, healthcare informatics with its expanding amount of routinely collected, electronic patient data comprises a huge potential for the exploitation of data for research purposes and future developments in personalised medicine. In order to avoid age discrimination, this should also include the utilisation of electronic patient data in the interest of older adults.

Over the last two decades, frailty was characterised as an age-associated disproportionate decline in physiological reserves leading to increased vulnerability to external stressors,² and shown to be an important predictor of negative health outcomes in older adults.³ Nonetheless, frailty is still underdiagnosed in acute care although frail older adults have more frequent and longer hospital stays, are



re-hospitalised more often and eventually die earlier than their non-frail counterparts.^{3,4}

The British Geriatrics Society issued a recommendation for routine frailty screening in geriatric outpatients in order to timely assess the risk of frailty on the health of older adults.⁵ Moreover, frailty is becoming more and more recognised as a useful concept for risk stratification in various medical specialties, from oncology to heart surgery.⁶ However, as the field is evolving, there has been no agreement either on the ideal conceptualisation of frailty or on a single best screening instrument over the past decades.⁷⁻¹⁰ This happened to be a major roadblock for the broader implementation of the frailty concept into patient care.¹¹ At the same time, assessing frailty systematically in clinical care might open up a window of opportunity for both improving patient care for older adults and accelerating research efforts for a better understanding of the underlying pathophysiology of frailty as a state or condition (ie, by a Frailty Index (FI) approach) and as a syndrome (ie, the frailty phenotype).¹⁰

Today, among the highly cited frailty conceptualisations, the frailty phenotype by Fried *et al*¹² and the deficit accumulation concept (ie, FI) by Mitnitski *et al*¹³ stand out as the two most extensively investigated approaches of frailty.¹⁴ As this two approaches measure different concepts of frailty (ie, a clinical syndrome vs a multi-system decline based index), their comparability may be limited. In addition, it should be taken into account that the phenotype usually requires clinical measurements, whereas a FI can be generated from available patient data collected during routine clinical practice. Therefore, deriving a FI from electronic health records (EHRs) data that are routinely collected, has the potential to expedite the routine identification of frail patients in acute hospital care in various medical specialties, as no additional resources are needed.¹⁵ This approach has been recently demonstrated by Cesari *et al* investigating a FI in an Italian cohort of hospitalised patients.¹⁶ With regard to the investigation of significant clinical endpoints including in-hospital mortality and length of stay (LOS) by an electronic Frailty Index (eFI), which has not been undertaken in hospitalised older adults in Switzerland so far, a comparative view on both frailty concepts contains the opportunity to provide important additional information.

The Swiss Frailty Network and Repository (SFNR) aims to establish a nationwide harmonised eFI consisting of 55 variables from routinely collected EHR data in patients aged 65 years and older at all five Swiss University Hospitals in order to investigate its predictive abilities in regard to LOS and in-hospital mortality. A secondary validation aim investigates the correlation of the eFI as a screening tool against the detection of frailty by a harmonised clinical Frailty Instrument (cFI) based on the Fried phenotype concept, in a subset of patients aged 65 years and older from acute geriatric care at all five Swiss University Hospitals' geriatric centres. In order to take into account the importance of cognitive impairment with regard to

frailty, we have added a short cognitive test as an additional component to the cFI.^{17,18} We will investigate the predictive abilities of both, the eFI and the cFI regarding two important outcomes in acute hospital care, LOS and in-hospital mortality. The development of a frailty data repository will in addition serve as a basic personalised health research infrastructure for future studies in older adults across all partner institutions.

The utilisation of routinely collected, electronic patient data is a major focus area in healthcare, and of growing interest in many acute care settings, including geriatric medicine. Frailty is highly prevalent in older patients and appears as a major driver of multiple negative outcomes in this population. Establishing a harmonised eFI from routinely collected EHR data is therefore a timely effort that will likely contribute to the improvement of care for older adult patients by early identifying those at increased risk for adverse outcomes.

The main deliverable of the SFNR will be to establish a nationwide eFI derived from routinely collected electronic patient data for older adults in Switzerland curated within the Swiss Personalized Health Network (SPHN) BioMedIT ecosystem. We aim to demonstrate the eFI's predictive ability for LOS and in-hospital mortality and investigate the comparative performance of the eFI in the detection of frailty against our cFI in a subset of patients admitted to acute geriatric care.

Our proposition of a systematic clinical evaluation of frailty using the cFI as a clinical research reference standard in all enrolled patients admitted to acute geriatric care at all five Swiss Academic geriatric centres is a secondary outcome of our collaboration that may lead to a more unified approach to the measurement of the frailty phenotype on the national level. Therefore, establishing the SFNR will likely advance both, the field of geriatric medicine and research in Switzerland. Incorporating frailty as a criterion in acute care will allow a systematic and personalised pre-therapeutic stratification of patients according to each patient's profile. This individualised approach will enhance the definition of person-based potential harms and benefits of interventions in various medical disciplines, ranging from emergency medicine and orthogeriatric units to cardiovascular surgery and comprehensive cancer care. We expect first results to be ready for scientific publication by mid 2022.

METHODS AND ANALYSIS

The SFNR is a joint effort by all five Swiss Academic Geriatric Departments (Universities of Basel, Bern, Geneva, Lausanne and Zurich and adjacent University Hospitals) that is funded by the SPHN (grant no. 2017DRI02), an initiative of the Swiss Federal Government, namely the State Secretariat for Education, Research and Innovation and the Federal Office of Public Health.¹⁹

The SFNR has five primary aims:

1. Reaching a consensus on a nationwide research reference standard to assess frailty clinically in geriatric

Table 1 Components of the SFNR clinical Frailty Instrument

Domain (item)	Operationalisation (test-based)	Cut-point (threshold)
Shrinking (weight loss)	Unintentional weight loss or loss of appetite; report of lose clothing, weight loss documented in patient chart	Any reported weight loss or loss of appetite or lose clothing or >5% last 6 months (from EHR)
Fatigue	Self-reported exhaustion measured by Geriatric Depression Scale (GDS) 4 item	≥2 Points on GDS-4 ^{31 32}
Slowness	Slow gait speed on standardised 4 m measurement from a standing start (best of two consecutive measurements)	Gait speed below 0.8 m/s
Weakness	Low hand grip strength measured by the Martin Vigorimeter (in Kilopascal), best of three consecutive trials at the dominant hand at time of assessment	Below the median of lowest 20% (by gender and age <75 and ≥75 years) compared with a sample of generally healthy Swiss older adults (from the DO-HEALTH study ^{33 3435})
Low activity level	Reported frequency of activities with moderate energy expenditure (question BR016_ModSprtsAct from SHARE questionnaire ³⁶)	Answer of 'less than once a week'
Cognition	Three item recall and clock drawing test (CDT)	Any error in recall or CDT indicates cognitive disturbance

EHR, electronic health record; SFNR, Swiss Frailty Network and Repository.

patients at all five partner sites (definition of cFI, goal 1), see [table 1](#).

2. Reaching a consensus on the candidate variables aggregating to a harmonised eFI from regularly collected electronic patient data extracted from the local clinical information systems (CISs) at all five sites (goal 2), [table 2](#).

3. Setting up of a frailty data hub for the collection, organisation and maintenance of coded data from all five centres including both, the cFI from patients in acute care seen by the geriatric teams at each site (related to goal 1) and the harmonised eFI (related to goal 2) from all patients aged 65 years and older at the partnering Swiss University Hospitals.

4. Investigating the correlation of the eFI as a screening tool against the cFI as a clinical criterion standard within the pooled data set from all five geriatric centres (association study).

5. Investigating whether the prognostic abilities differ between the cFI and the eFI with regard to the prediction of LOS and in-hospital mortality in acute geriatric care (correlation study).

Sample size calculation

For our study, the estimated total sample size of 1000–1500 patients within a 12-month planned period was based on the two primary endpoints, hospital LOS and in-hospital mortality. In a prior study, Hope *et al* found a median (IQR) LOS in the hospital for non-frail and frail individuals to be 13 (IQR 8–23) days and 17 (IQR 10–30) days, respectively.²⁰ Assuming symmetry, this translates to a mean (SD) of 13 (SD=(23–8)/1.35=11.1) days for non-frail individuals and 17 (14.8) days for frail individuals.²¹ Another study investigating older adult medical inpatients found a range in LOS between 4.2 and 7.8 along a

FI score based on a comprehensive geriatric assessment.²² In addition, a systematic review and meta-analysis of nine observational studies investigating outcomes in general surgery reported a mean LOS of 9.6 days (95% CI: 6.2 to 12.9) in frail and 6.4 days (4.9 to 7.9) in non-frail patients.²³ Conservatively assuming 20% of older adults in acute care are frail (expected range from literature 20%–50%)²⁴ and assuming a difference in hospital LOS of 4 days, a total of 418 persons (92 frail, 326 non-frail) would be needed to achieve 80% power at the 0.05 alpha level. Using a more conservative estimate of detecting a difference in hospital LOS of 2 days, 1655 (364 frail, 1291 non-frail) individuals would be needed to achieve 80% power at the 0.05 alpha level. Vermeiren *et al* conducted a meta-analysis of 24 prospective studies comprising over 150 000 individuals and found frailty to increase the likelihood of mortality more than twofold (OR 2.34 (1.77 to 3.09)).³ We assume 20% of individuals are frail, and leave room for a greater degree of uncertainty (wider CI, CI 1.42 to 3.91) since this is a single study as opposed to a large meta-analysis comprising many individuals. For a mortality rate of 5% in non-frail individuals, a total of 1077 persons (237 frail, 840 non-frail) would be required to detect an OR=2.34 at the 0.05 confidence level.

In summary, we consider a sample size of approximately 200–300 patients enrolled at each of the five partnering sites over the planned 12-month period sufficient to answer our research questions. However, the number of recruited participants at each site might not be equally distributed and differ largely due to the local environments and in-patient capacities. Of note, the primary analysis will be performed on the total sample of 1000–1500 patients.

Table 2 Variables and coding of the SFNR electronic Frailty Index (eFI)

System	Source	Variables (no.)	Cut-point/coding
Functional impairments	Electronic health records (EHRs): electronic nursing charts (NANDA)	1. Chronic constipation 2. Feeling tired 3. Problems with falling/staying asleep 4. Problems with sleep-awake cycle 5. Urinary incontinence 6. Help getting on/off bed 7. Help going to the toilet 8. Help walking 9. History of falls 10. Inability to walk stairs 11. Irregular gait pattern 12. Patient using walking equipment/aid 13. Problems getting dressed 14. Problems with bathing 15. Clouding or delirium	Yes=1, no=0 impaired=1, normal=0
Comorbidities	EHRs: diagnosis list medication use	16. Food intake 17. Active malignancy 18. Hearing impairment 19. History of osteoporosis 20. Cardiac arrhythmias 21. Coronary heart disease 22. Pressure sores (decubital ulcers) 23. Diabetes mellitus 24. History of seizures 25. History of stroke 26. Memory impairment 27. Chronic obstructive lung disease 28. Use of anticoagulation medication 29. Use of antiplatelet medication 30. Polypharmacy (>5 drugs) 31. Use of sedative, hypnotic and/or neuroleptic drugs	Presence (yes)=1, absence (no)=0
Laboratory results	Primary laboratory System	32. Haematocrit 33. Haemoglobin 34. Platelet count 35. Red cell volume (MCV) 36. Creatinine 37. Urea 38. Thyrotropin 39. C-reactive protein 40. Lymphocyte total count 41. High-density lipoprotein 42. Potassium 43. Sodium 44. Albumin 45. Blood glucose 46. Cholesterol	<35%=1, ≥35%=0 Serum concentration above or below reference range=1, within=0 <3.9 or >15 mmol/L=1, other=0 >7 or <3.5 mmol/L=1, other=0
Vital signs	EHRs	47. Body temperature 48. Diastolic blood pressure 49. Heart rate (pulse) 50. Systolic blood pressure 51. Oxygen saturation (SpO ₂) 52. Patient requires supplemental oxygen	<36,3°C=1, ≥36,3°C=0 >90mmHg=1, ≤90 mmHg=0 <60 or >99 BPM=1, other=0 >140mmHg=1, ≤140 mmHg=0 <90%=1, ≥90%=0 yes=1, no=0
Other	EHRs	53. Age 54. Body mass index 55. Patient reports being in pain	>80=1, ≤80=0 <18.5 or ≥30=1; >25 and <30=0.5, other=0 yes=1, no=0

SFNR, Swiss Frailty Network and Repository.

Data collection

The data collection for the components of the cFI will take place within the first 4 days on admission to acute geriatric care at all partner sites by certified examiners following a standardised protocol. For calculating the eFI, only variables available from within 4 days on admission will be retrieved from the EHR and included to the dataset.

Statistical analysis

In regard to the eFI's variables, each will be scored as either '1', that is, presence of the deficit or '0', that is, absence of the deficit, except for body mass index (<18.5 or $\geq 30 = 1$, >25 and $<30 = 0.5$, other=0), see [table 2](#) for full list of variables. We will use validated cut-points regarding the classification of the degree of robustness or frailty from prior literature.^{25 26} We will additionally test, whether eFI scores differ between the classification of frail/pre-frail and robust by the cFI in our subsample from acute geriatric care. To evaluate the ability of the eFI screening tool to correctly classify each patient as frail, pre-frail or non-frail in regard to the phenotypic approach, we will calculate the sensitivity, specificity, as well as positive and negative predictive values of the eFI (pre-defined cut-offs and tertiles) against the cFI.²⁷ Each potential threshold will be applied to the continuous total sum scores of the eFI to classify frail vs non-frail participants. The resulting true positive rate (sensitivity) and false positive rate (1-specificity) will be determined using the cFI as the reference. A receiver operating characteristic (ROC) curve will be constructed for all possible thresholds of the eFI. Discriminative ability will be estimated based on the area under the ROC curve and associated C statistics.

Hospital LOS in frail and non-frail individuals (classified by eFI and cFI) will be summarised using mean, median, SD, IQR, minimum and maximum. Differences in hospital LOS between frail and non-frail individuals will be tested using a two-sided independent *t* test, or Mann-Whitney U test if the data is skewed, at the 0.05 level. In-hospital mortality rates will be calculated for the overall sample as well as for frail and non-frail subgroups. Logistic regression will be used to quantify the association of frail (vs non-frail) on in-hospital mortality.

Progress to date

In the first year of the project, consensus was reached among the project partners regarding the composition and scoring of the cFI. At the same time, the 55 variables summarised in the eFI were defined and harmonised. In the second year, the local requirements for the provision of the data to be collected were analysed and the required IT infrastructure for secure data processing and delivery was set up. At the same time, the project-related data infrastructure within the BioMedIT network was defined and made available by SPHN. Enrolment of first participants into the study began in June 2020.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of our study. Participants will be informed regarding the detailed results of our study only on request. However, the results will be disseminated to the public according to the SPHN's dissemination policy and by published articles.

ETHICS AND DISSEMINATION

For the association study, with regard to the eFI, we will use data from consecutive patients aged 65 years and older admitted to acute care on various departments of the partnering university hospitals from a determined starting date and with available written informed consent for further use of routine clinical data. For the correlation study, we will use data from all patients aged 65 years and older recruited from acute geriatric care units who agreed to participate in the study by informed consent.

All ethics committees of the involved partner sites, chaired by the ethics committee of the Canton of Zurich have approved our study (swissethics BASEC-ID 2019-00445).

SPHN IT ecosystem

Our project's hosting initiative, the SPHN, is currently developing a nationwide healthcare data ecosystem in Switzerland to work towards interoperability of data from local information systems, for example, clinical data management systems in enabling an effective exchange of patient data (eg, disease phenotypes) for research with the ultimate goal of advancing personalised medicine.^{28 29} Our project will support and build on this effort as a driver project. In a first step, the agreed set of eFI variables was submitted to the SPHN Clinical Semantic Interoperability Working Group, which has integrated the variables in a Swiss wide core dataset and is defining for each variable in which format they shall be shared and which additional (meta-) data are needed for optimal interoperability. The data of the test-based cFI will be collected in a standardised and centralised electronic Case Report Form in REDCap (Vanderbilt University, Nashville, Tennessee, USA) or in the CIS (EHR).

Next, our collected data (eFI and cFI) will be locally pre-processed by the clinical data warehouse teams. In particular, patient IDs will be mapped and de-identified before sharing to respect data privacy regulations.¹⁹ Additionally, a standardised format for data transfer defined by a Data Coordination Center (DCC) will be used in order to allow interoperability. We will use the novel Swiss BioMedIT-Node secure data infrastructure currently under development by the Swiss Institute of Bioinformatics and managed by the Personalized Health Informatics Group and coordinated by the DCC as part of SPHN.³⁰ The de-identified data will be encrypted with a secure, standard mechanism (GPG, GNU Privacy Guard) and sent via secure transfer to BioMedIT.



On BioMedIT, the analysis of the data will take place using state of the art software and tools thereby ensuring highest security levels for access to data, processing and sharing. FAIR data principles (findability, accessibility, interoperability, reusability) will be respected and ensured throughout the project in accordance with SPHN strategy.

Author affiliations

- ¹Department of Geriatrics, University Hospital Zurich, Zurich, Switzerland
²Centre on Aging and Mobility, University Hospital Zurich and University of Zurich, Zurich, Switzerland
³Research Data Service Center, Clinical Trails Center, University Hospital Zurich, Zurich, Switzerland
⁴Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
⁵Department of Epidemiology and Health Systems, Center for Primary Care and Public Health, Lausanne, Switzerland
⁶Service of Geriatric Medicine and Geriatric Rehabilitation, Lausanne University Hospital, Lausanne, Switzerland
⁷Universitäre Altersmedizin FELIX PLATTER, Basel, Switzerland
⁸Department of Geriatrics, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland
⁹Division of Geriatrics, Department of Internal Medicine, Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland
¹⁰Department of Rehabilitation and Geriatrics, University Hospitals Geneva, Geneva, Switzerland
¹¹Universität Basel, Basel, Switzerland

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ORCID iDs

Michael Gagesch <http://orcid.org/0000-0003-3089-5768>
 Christophe J Büla <http://orcid.org/0000-0002-7501-3442>
 Heike A Bischoff-Ferrari <http://orcid.org/0000-0002-4554-658X>

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