



Project Final Publishable Summary

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Final publishable summary

SENATOR



Project title: Development and clinical trials of a new Software ENGINE for the Assessment & optimization of drug and non-drug Therapy in Older peRsons

Website: <http://www.senator-project.eu/home/>

Contractors involved (SENATOR consortium):

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1.1 Executive summary

Inappropriate prescribing and associated adverse pharmacotherapy are known to be common in multi-morbid older people exposed to polypharmacy (multiple medications at once). STOPP/START criteria designed to identify instances of potentially inappropriate medications or PIM's (STOPP) and potential prescribing omissions or PPO's (START) formed the basis of the SENATOR project. Single centre clinical trials carried out in Cork where STOPP/START criteria were developed prior to SENATOR indicated that STOPP/START criteria as an intervention significantly reduced inappropriate prescribing, adverse drug reactions (ADRs) and monthly medication costs in multi-morbid older patients with polypharmacy. Other trials carried out in Belgium and Israel in recent years using STOPP/START criteria as an intervention demonstrated significant reductions in inappropriate medication, polypharmacy, medication costs and falls in multi-morbid older people compared to standard pharmaceutical care. The central aim of SENATOR was to design, develop and validate a software engine that included essential features for minimizing adverse pharmacotherapy (including STOPP/START criteria) in older multi-morbid patients. The SENATOR software engine would then be evaluated in tandem with standard pharmaceutical care compared to standard pharmaceutical care alone in a larger scale multi-centre randomized

controlled clinical trial involving 6 different European countries. SENATOR also examined the evidence base for the various therapies in 15 common “ONTOP” conditions commonly encountered in older multi-morbid people.

Phase 1 (observational) of the SENATOR trial involved 644 patients enrolled from the 6 clinical sites in which we tested (i) a novel ADR ascertainment method based on a Trigger List of common manifestations of ADRs in older people with multi-morbidity, and (ii) a complex electronic case report form for its capacity to store and link individual patient data to a large Drug File database. Phase 2, the randomization intervention phase, involved 1537 older patients hospitalized with acute illness under the care of clinicians other than geriatricians, clinical pharmacologists, palliative medicine physicians, oncologists, haematologists, psychiatrists and intensive care specialists. Patients were randomized to standard pharmaceutical care (control arm) or standard pharmaceutical care plus a single time point SENATOR software-generated medication advice report issued to senior attending medical staff (intervention arm). Decisions to adjust intervention arm patients’ pharmacotherapy according to SENATOR report advice points lay with the attending clinicians alone, as per the study protocol. Phase 2 primary and secondary endpoints related to incident ADRs. Phase 1 results confirmed the previously reported high incidence of ADRs in older patients with multi-morbidity/polypharmacy hospitalized with acute illness under the care of specialist services other than geriatric medicine and clinical pharmacology i.e. 21.6%. Phase 2 reaffirmed this finding i.e. an overall 24.7% ADR incidence in the Phase 2 population of 1537 consisting of 765 control and 772 intervention patients. Primary and secondary endpoints were assessed at 14 days or hospital discharge, whichever came first. Tertiary endpoints, focused on the potential economic benefits from SENATOR software, including quality of life (EQ-5D-5L scale), rehospitalisation and composite healthcare utilization were calculated at 12 weeks post-randomization. Statistical analysis found no significant differences between the control and intervention populations for primary or secondary endpoints. Tertiary endpoint analysis, whilst showing no significant differences between the trial arms, did indicate that SENATOR would likely be a cost-effective intervention. However, crucially, adherence by attending clinicians/prescribers with SENATOR software advice points was only 15% i.e. approximately 85% of SENATOR report advice points were not implemented. Hence, SENATOR as a pragmatic trial by design is essentially a negative trial. Positive outcomes from the SENATOR project include:

- (i) A novel method for detecting ADRs in multi-morbid older people i.e. those at highest risk form ADRs, showing a non-trivial ADR incidence of approximately 25% in these people when hospitalized with acute illness. Given that multi-morbid older people are the largest patient group accessing acute hospital services, this ADR incidence represents a major patient safety issue that warrants further study towards prevention.
- (ii) A novel software engine that deploys STOPP/START criteria as well as complementary non-trivial drug-drug and drug-disease interactions and advice points on non-drug therapies for the most common age-related syndromes.
- (iii) A compendium of the most up-to-date, evidence-based therapies for the 15 most common chronic medical conditions experienced by older people i.e. the ONTOP compendium.

1.2 Summary description of project context and objectives:

Background and Aims

Multi-morbidity i.e. the presence of multiple chronic medical conditions in the same person is a constant of older people, particularly persons aged over 75. Since population ageing is a global as well as a European phenomenon, the prevalence of multi-morbidity is increasing across the EU as well as globally. Multi-morbidity of late life inevitably brings with polypharmacy i.e. multiple long-term medications. It is a generally accepted fact that polypharmacy in turn engenders inappropriate prescribing (IP) which in turn predisposes to adverse drug reactions (ADRs) and adverse drug events (ADEs). When older people experience polypharmacy-related ADRs and ADEs, the likelihood of serious morbidity is greater than in younger patients. In addition, the symptoms arising from ADRs and ADEs in older people are often non-specific, such that ADRs and ADEs can go unrecognized and thereby be misinterpreted as new pathologies. These misdiagnosed new pathologies arising from the adversity caused by one drug can lead to further prescriptions of other drugs, so-called ‘prescribing cascades’. Quite apart from the avoidable morbidity associated with inappropriate prescribing and associated ADRs/ADEs in older people,

inappropriate prescribing and its consequences in older people is highly expensive. This is because IP-associated ADRs/ADEs leads to excess healthcare utilization and prolonged hospitalization, quite apart from the financial wastage arising from prescriptions that should have been avoided in the first place.

The prevalence of IP in older people is unacceptably high in every clinical setting. Data from Ireland in the last decade show that the prevalence of one or more potentially inappropriate medications (PIMs) in older multi-morbid people in the community-dwelling independent population interacting with primary care is 22%, in the acute general hospital it is 33%-40% whilst in the long-term nursing home setting it is 60%-70%. Potential prescribing omissions (PPOs) i.e. the omission of potentially beneficial medication for no valid clinical reason is even more prevalent than PIMs, i.e. 22% in primary care, 57%-60% in hospital care and 70%-80% in nursing home care in Ireland. A hospital based study involving older multi-morbid patients in 6 European countries showed that the high rate of PIMs and PPOs was not confined to Ireland. In some of these European medical centres, the prevalence of PIMs and PPOs was even higher than in Ireland.

STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria had been developed in University College Cork in the mid-2000s and were published in fully validated form in early 2008. Early clinical trials carried out in Cork between 2007 and 2012 had shown that STOPP/START criteria used in tandem as a clinical intervention could significantly improve medication appropriateness, reduce the incidence of ADRs experienced by multi-morbid older people in hospital and reduce average monthly medication costs. However, these trials had limitations in that they were single centre, not double-blinded and of smaller scale. When the FP7 Health 2012.2.2.2-2 research call was published in 2011, there was specific mention of "elderly people with multiple disease" (i.e. multi-morbidity), a "focus on drug therapy and other interventions" in this patient population and desired outcomes of "treatments better suited to the needs of older people, lowering healthcare costs and engaging in the pre-normative setting of geriatric medicines". These were the principal considerations for the SENATOR consortium when it was set up and the project was initiated.

The principal aims of the SENATOR project were:

- (i) To design and build a novel software (called "SENATOR") capable of deploying STOPP/START criteria, drug-drug constraints, drug-disease constraints and non-drug therapy advice points.
- (ii) To validate the SENATOR software by comparison with a Gold Standard of two experienced physicians deploying STOPP/START criteria, drug-drug constraints and drug-disease constraints without software support i.e. using paper versions of STOPP/START criteria and drug-drug constraints and drug-disease constraints.
- (iii) To validate a novel method of ADR detection and verification in multi-morbid older people.
- (iv) To design a clinical trial comparing standard pharmaceutical care versus standard pharmaceutical care plus SENATOR-software medication optimization in multi-morbid older people admitted to hospital with various acute medical and surgical illnesses under the care of attending clinicians other than specialists in geriatric medicine and clinical pharmacology in particular (as well as specialists in palliative medicine, oncology, haematology, psychiatry and intensive care). The aim of the SENATOR trial was to examine the effect, if any, of SENATOR software-generated advice reports on the incidence of ADRs in the target population during the index hospitalization (primary endpoint). The SENATOR trial was also designed to examine the impact (if any) of SENATOR advice reports on quality of life, healthcare utilization and rehospitalisation in the intervention population compared to controls over a period of 12 weeks post-randomization.
- (v) To create a compendium of evidence-based non-drug therapies in 15 common geriatric syndromes; this compendium was to be called ONTOP (Optimal evidence-based Non-drug Therapies in Older People"). The rationale for ONTOP was to establish which non-drug therapies had a firm evidence base such that they could be recommended in tandem with optimized drug therapy in older people with multi-morbid illness.

Work strategy and general description

The SENATOR project was divided into 12 interconnecting work packages, as follows:

WP01 Design & validation of the ADR Risk in Older Persons (ADRROP) scale: The aim of WP01 was to devise and validate an ADR prediction scale from a database of 2217 older patients who were studied in detail in terms of defining whether they had experienced ADRs/ADEs at admission to hospital or during hospitalization with acute unselected illness under the care of clinicians other than specialist geriatricians or clinical pharmacologists. Depending on predictive power of ADRROP, we further planned to refine ADRROP from the high quality and high precision ADR definition from the SENATOR trial database.

WP02 Definition of Optimal evidence-based Non-drug Therapies in Older People (ONTOP): The aim of ONTOP was to create a novel compendium of non-drug therapies for 15 common chronic conditions affecting older people i.e. delirium, pressure ulcers, falls, dementia, heart failure, urinary incontinence, sarcopenia, orthostatic hypotension, stroke, diabetes, malnutrition, COPD, vision impairment, hearing impairment, and osteoarthritis. The ONTOP compendium would provide up-to-date information on non-drug therapies to complement optimized drug therapies in older people with multi-morbidity. ONTOP would be created by systematically examining the published systematic review literature dealing with the non-drug therapies in the 15 conditions using established PICO (Population, Intervention, Comparison and Outcomes) and GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodologies for data extraction and assessment from published systematic reviews. As a proof-of-concept, ONTOP recommendations for delirium would be inserted into SENATOR software-generated advice reports in intervention arm patients at risk of delirium in the SENATOR trial.

WP03 Data collection on European drug availability, pricing and policies: The aim of WP03 was to create an electronic Drug File that could be used to interface with the SENATOR software so that STOPP and START criteria could be reliably deployed as well as identifying potentially serious adverse drug-drug and drug-disease interactions from existing databases. For SENATOR software to function effectively, all medications available in all formularies in the 6 participating countries would be coded appropriately and subsequently connected to ICD-10 disease codes as the means of activating potentially adverse prescribing within the SENATOR trial electronic case report form (eCRF). STOPP and START rules, as well as potentially serious adverse drug-drug and drug-disease interactions, where applicable, would be listed in a structured way in the SENATOR software-generated advice report which was the essence of the intervention in the SENATOR clinical trial. Ideally, up-to-date medication pricing information would also be included in the SENATOR advice report to facilitate lowest price medication selection by the attending physician.

WP04 Design & construction of SENATOR software: In the absence of commercially available software with the capability of deploying the full set of STOPP/START criteria in tandem with drug-drug and drug-disease interactions, it was necessary to design and build the SENATOR software engine as the intervention tool to be used in the clinical trial embedded in this project. WP04 also entailed the challenge of creating a working interface between SENATOR software and the eCRF and the Drug File. WP04 was led by Clanwilliam Health®, a major healthcare software company based in Dublin.

WP05 Pilot testing and scientific validation of SENATOR: An essential requirement prior to proceeding to the SENATOR randomized controlled clinical trial (c.f. WP08) was the prior testing and validation of SENATOR software. Thus, in WP05 the focus was to put novel SENATOR software to the test using the data on 20 clinical cases, each describing multi-morbid older patients with polypharmacy. With the information provided, SENATOR generated bespoke medication recommendations in each of the 20 cases. The performance of SENATOR software would, if to be deemed suitable for use in the clinical trial, need to closely approximate to the performance of the Gold Standard. The Gold Standard was application of STOPP/START criteria as well as detection of potentially serious adverse drug-drug and drug-disease interactions by two physicians trained in geriatric medicine and pharmacotherapy who reached consensus. Once the performance of SENATOR software was demonstrably matching closely that of the Gold Standard, it was appropriate to proceed with deploying SENATOR software in the randomized clinical trial.

WP06 Translation & language validation of SENATOR: Because the SENATOR trial was to be carried out in 6 clinical centres, 4 of which involving the local language being other than English, it was necessary to ensure that the eCRF and SENATOR software were appropriately translated from English into Spanish, Italian, Dutch and Icelandic. Similarly, the information leaflets for attending clinicians and patients had to be presented in the local languages and this task was also an integral part of WP06. Data output from SENATOR in the 4 non-English languages also had to be validated compared to the English language output which was the Gold Standard.

WP07 Trial Organization & Governance: SENATOR was a complex pragmatic trial involving a complex intervention and primary and secondary endpoints that were challenging to ascertain. The trial governance and organization was, accordingly, complex and intricate. The study protocol for the SENATOR trial was a key objective of WP07 as was the design and construction of the eCRF which involved a software system capable of collecting demographic, socioeconomic, diagnosis, medication, cognitive status, functional status and comorbidity status details of all patients. It was decided to undertake an observation Phase 1 study prior to the randomization clinical trial Phase 2, the purpose of Phase 1 being to test the eCRF, to test the ADR ascertainment and verification algorithm, and to calculate the ADR incidence to facilitate more precise power calculation of Phase 2. Phase 1 would also provide the necessary information regarding which parts of the eCRF were absolutely essential to retain or modify in order to address the core questions of the randomization clinical trial in Phase 2. Finally, any significant problems arising with the eCRF and ADR ascertainment algorithm in Phase 1 would be fully addressed and overcome prior to Phase 2. WP07 also involved the setting up and operation of a SENATOR Clinical Trial Coordination centre at UCC which would become the host and repository of all SENATOR trial data for future analysis. Finally, all matters relating to trial oversight and monitoring would be dealt with in WP07 in keeping with Good Clinical Practice relating to clinical trials.

WP08 Randomized Controlled Trial (RCT) of SENATOR versus 'Standard Care': The randomized controlled clinical trial was the centrepiece of the SENATOR project. In the clinical trial, there were two phases. Phase 1 was designed as an observation phase in which the eCRF was tested as well as the novel ADR ascertainment system which was based on a so-called 'Trigger List' of the most common clinical manifestations of ADRs in older people; the Trigger list had been used in a previous study carried out in Cork and was found to capture over 80% of verifiable non-trivial ADRs. The Trigger List had to be re-validated as part of Phase 1 prior to Phase 2, the randomization phase. We opted for a conventional randomization plan on a 1:1 intervention:control patient ratio. Power calculations indicated that a target number of 1800 patients was needed to show a clinically significant difference between intervention and control groups in Phase 2. Phase 2 was designed such that all patients enrolled would receive standard pharmaceutical care as it currently existed in each of the 6 participating clinical centres. In the intervention group, patients attending clinicians would receive a SENATOR software-generated advice report with specific advice points based on STOPP and START criteria that applied as well as potentially serious drug-drug and drug-disease interactions; in addition, as a proof-of-concept, SENATOR reports would include advice regarding non-pharmacological treatment regarding the prevention of delirium in at-risk patients (i.e. the whole of the intervention arm patients). The intervention would be applied within 60 hours of admission and at a single time point only. The primary and secondary endpoint ascertainment were to be carried out at 14 days post-randomization or at hospital discharge in all patients, whichever came first. Tertiary endpoints and economic data were to be collected at 12 weeks +/- 2 weeks post-randomization.

WP09 Ethics & Safety Monitoring: As with all clinical trials, particularly one involving potentially vulnerable older people, the SENATOR trial required comprehensive ethical and safety oversight and monitoring. Ethical oversight was provided by an independent Ethics & Safety Review Group (ESRG) made up of two senior clinicians, a legal representative trained in bioethics and an older patient lay advocate (in this case, a former CEO of Age Action Ireland, a long established non-governmental organization). In addition, there was an independent Scientific Advisory Board (SAB) to oversee and advise on all matters relating to the scientific aspects of the SENATOR project; the SAB included five recently retired senior academic geriatricians, a professor of clinical pharmacology and a professor of clinical pharmacy from a range of European countries (Ireland, UK, Netherlands, Spain, Belgium). Following the establishment of the ESRG and SAB, WP09 required formal periodic reporting by the ESRG to the SAB as well as establishment of a clinical trial risk registry to ensure patient safety was a core element

of the SENATOR trial. All documentation relating to the operation of the SENATOR trial was reviewed to the ESRG to ensure high standards of safety monitoring and its findings were subsequently reported to the SAB for review and approval.

WP10 Data Management: The remit of SENATOR trial data management was shared between ClinInfo@ the SME with responsibility for construction of the eCRF and UCC Clinical Research Facility in Cork (CRFC). WP10 involved trial patient randomization following enrolment, monitoring of all data entry for accuracy, data quality oversight, electronic back-up of all patient data and transfer of trial data to the UCC co-ordinating centre for data cleaning and statistical analysis at the end of the trial. WP10 also had shared responsibility for ensuring that electronic databases interfaced satisfactorily i.e. eCRF with the Drug File (ATC coded medications), eCRF with ICD-10 disease codes. Furthermore, all data generated by the eCRF had to be confirmed for accuracy and stored appropriately and with sufficiently high-level security. Generation of the final clinical trial report, the most important document in the entire project, was the core responsibility of WP10.

WP11 Economic Analysis of SENATOR'S clinical efficacy: WP11 was designed to (i) undertake a detailed literature review of the economic aspects of medication optimization in multi-morbid older people and (ii) measure the economic impact (if any) of the SENATOR software intervention compared to standard care. This WP was led by experts in health economics from University of East Anglia based at Norwich, UK. The eCRF included quality of life measurement (using EQ-5D-5L), indicators of medication and hospitalization costs, and 12 week post-enrolment follow-up indicators of healthcare utilization. From cost analysis and sensitivity analysis, WP11 would establish the economic benefit (if any) arising from the SENATOR intervention.

WP12: Project Management, Communication & Dissemination: A third SME, ARTTIC, was responsible for WP12 replacing the participant GABO:mi which terminated its participation on 30 June 2016. ARTTIC has more than 30 years of experience in managing collaborative research and innovation projects, including the biomedical sector. In collaboration with the co-ordinating centre at UCC, ARTTIC managed the last two periods of the project until the completion stage. Within SENATOR, ARTTIC continued the responsibilities of maintaining and updating the project website <https://www.senator-project.eu/home/>, online since 2013, and the project document database and repository (called 'milliarium'), organization of project consortium teleconferences, the consortium General Assembly meetings, consolidating reporting documentation to the EC and dissemination and communication of project results.

Management structure and procedures

Prof. Denis O'Mahony from the University College Cork is the Project Coordinator of SENATOR. He is and has been the intermediary between the European Commission and the Consortium as well as the supervisor of the overall progress of the project. Central Office and Project Office (01UCC and 14ART) of SENATOR are established by and based at the Coordinator site in Cork (UCC Clinical Research Facility) and the ARTTIC branch office in Munich, respectively. They are concerned with the coordination and support of all research activities (scientific management) and management tasks relating the coordination of the project. To facilitate the organization and management, the Scientific Programme of the project is structured in 12 work packages (WPs). Each work package is headed and coordinated by an experienced principal investigator as work package lead and a deputy leader. The WP leaders are responsible for the management of their WPs. The WP leader supervises and adjusts the process flow and has an integrating function being responsible for engaging and communicating with all partners in the WP. The WP leader reports on the progress of the WP in relation to the deliverables and milestones achieved and any issues causing delays. To ensure and document this, the WP leader periodically sends an internal Interim Report to the Steering Committee (STC) in a structured form and reports to the General Assembly. The STC is made up of the WP leaders and is in charge of monitoring all activities towards the objectives of the project in order to deliver it as promised, on time and within the budget. The General Assembly consists of one representative of each Participant with authority to vote. All other (non-voting) researchers working for this project may join the meetings and discussions.

Objectives of SENATOR:

- To devise and validate a new ADR Risk scale in Older People (acronym, ADRROP) to help identify older people at higher risk from ADRs.
- To devise a database compendium of Optimal evidence-based Non-pharmacological Therapies in Older People (acronym, ONTOP) to complement pharmacological therapy.
- To design and validate a Software Engine for the Assessment and optimization of pharmacological and non-pharmacological Therapy in Older peRsons with multi-morbidity (acronym, SENATOR).
- To develop the SENATOR electronic tool as a commercial software product, if shown to have efficacy.
- To assess the clinical value of SENATOR in a population of hospitalized older people with chronic multi-morbid illness compared to current standard clinical care delivered by clinical staff who are not specialized in Geriatric Medicine. For proper assessment of SENATOR, a multi-centre randomized controlled clinical trial is clearly required.
- To assess the economic value of SENATOR deployment compared to current standard clinical care.

1.3 Description of the main S&T results/foregrounds of SENATOR

WP01 – Design and Validation of the ADR Risk Scale

ADRROP version 1 (WP01.01)

Background

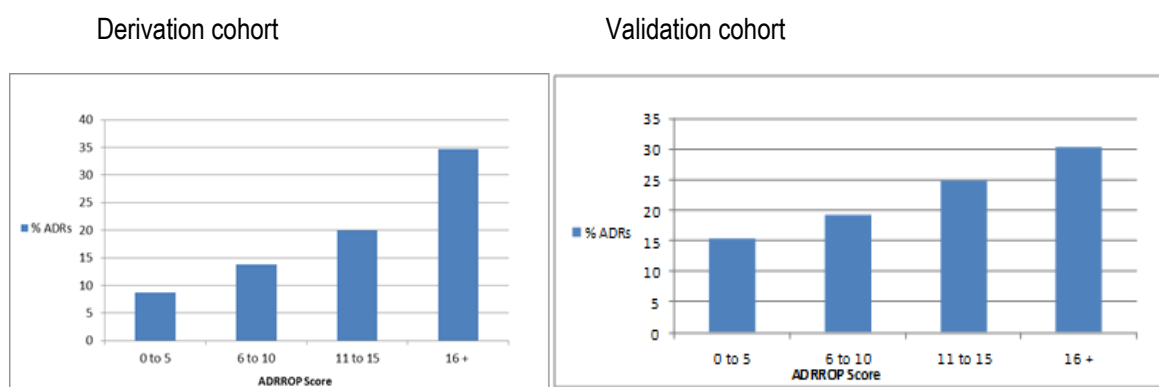
The essential aim of WP01 was to examine the possibility of creating a scale to predict adverse drug reactions (ADRs) in older patients with multi-morbidity and associated polypharmacy. This was based on the same principles applied in the GerontoNet ADR risk scale published in 2010 (1). In that study, Onder et al. used a retrospective database of almost 6000 older people in several Italian hospitals to derive an ADR risk prediction scale based on statistically significant ADR prediction variables. The GerontoNet ADR risk scale was validated prospectively in 483 older multi-morbid patients with polypharmacy admitted to 4 large hospitals in Italy, UK, Belgium and The Netherlands. The area-under-the-curve (AUC) statistic in the validation study was 0.70 (95% CI, 0.63-0.78), consistent with 'good' ADR prediction with the GerontoNet ADR risk scale. However, in a follow-up external validation study undertaken in Cork (2), ADR prediction using the GerontoNet ADR risk scale in 513 comparable multi-morbid older people admitted with unselected acute illness was found to be 'modest', with an AUC statistic of 0.62 (95% CI: 0.57–0.68). In this work package, we aimed to create a new ADR risk prediction scale aimed at integrating it into the SENATOR software provided the risk scale was found to have at least 'good' prediction i.e. $AUC > 0.70$.

Methods

The new ADR risk prediction scale was called ADRROP (ADR Risk in Older People) and was based on identifiable independent ADR risk variables from a combined database of 4 separate prospective studies involving multi-morbid older people older patients admitted to Cork University Hospital between 2007 and 2010. In these 4 separate prospective studies, ADRs were defined very accurately and particular drug causality was established precisely using WHO-UMC criteria. ADRROP version 1 is described in detail in a recent publication from the SENATOR consortium (2; Eur Ger Med 2018). In essence, the combined database included 2217 older patients. The database was divided into derivation (approximately 3/4 of all patients) and validation (approximately 1/4 of all patients) cohorts. Independent risk factors were derived from the derivation cohort using multiple logistic regression analysis. The odd ratios associated with each independent ADR risk factor were then used to construct the ADRROP scale, with the odds of ADRs associated with each risk factor rounded off to the nearest integer which reflected the relative weighting of each risk factor within the scale (following the same principles of the GerontoNet scale). Face validity was established in the derivation and validation cohorts by means of examining the percentages of patients experiencing ADRs in relation to ascending ADRROP score. For comparison with ADRROP version 1, we applied the GerontoNet ADR risk scale to the combined derivation and validation cohorts and calculated the ADR predictive power from further AUC analysis.

Results

Stepwise multiple logistic regression analysis of the derivation cohort patients identified the following independent ADR risk factors and their odds ratios (OR, 95% confidence limits): female sex (1.241, 0.961-1.602), age > 70 years versus age 65-70 (1.546, 1.051-2.327), estimated GFR < 30 ml/min/1.73m² (1.512, 1.030-2.221), assistance required for ≥ 1 daily activity (1.668, 1.279-2.176), ≥ 4 co-morbidities (1.523, 1.090-2.128), liver disease (2.259, 1.307-3.904), presence and number of STOPP criteria-defined potentially inappropriate medications (1.471, 1.097-1.972 for 1 STOPP drug; 2.693, 1.983-3.655 for ≥2STOPP drugs), and ≥1 fall in the previous year 1.369, 1.068-1.754). We constructed ADRROP version 1 from these variables, initially with a score range of 0 – 13.5, the points on the scale assigned to each risk factor being directly related to the odds ratios relevant to each significant ADR risk factor. For example, female sex was assigned a score of 1.0, this being the closest number within 0.5 to the odds ratio of 1.241. Similarly, liver disease was assigned a score of 2.5. For convenience and to deal in whole numbers, the scores assigned to each risk factor within ADRROP were doubled to give an ADRROP score range of 0 to 27. Face validity was established in both the derivation cohort (Figure 1) and the validation cohort (Figure 2). Figure 1: ADRROP score (x-axis) plotted against likelihood of ADR occurrence in the derivation cohort (n=1627) and validation cohort (n=530).



The AUC values for ADR prediction were 0.623 (95% CI: 0.598 – 0.665) in the derivation cohort and 0.592 (95% CI: 0.532 – 0.652) in the validation cohort. Applying the GerontoNet scale to the combined cohorts yielded an AUC of 0.566 (95% CI 0.537 – 0.596) i.e. poor ADR prediction by both ADRROP version 1 and GerontoNet ADR risk scales.

ADRRROP version 2

When ADRROP version 1 was found to have poor ADR prediction, we re-evaluated the prospective data from SENATOR Phase 2 which involved detailed ADR assessment in 1537 randomized patients. Using similar methodology to that described above for ADRROP version 1, we identified those independent risk factors for incident ADRs; from these risk factors, we derived a revised version of the ADR risk scale i.e. ADRROP version 2. In SENATOR Phase 2, the following were the odds ratios (with 95% confidence limits) for the ADR risk factors: female sex 1.40 (1.10-1.78), age > 70 years 1.31 (0.93-1.90), assistance required for ≥ 1 daily activity 0.87 (0.60-1.23), ≥1 fall in the previous year 0.92 (0.72-1.18), ≥4 co-morbidities 1.36 (0.21-26.29, estimated GFR < 30 ml/min/1.73m² 1.42 (0.98-2.02), liver disease 1.13 (0.81-1.56), 1 STOPP drug 0.83 (0.54-1.28), ≥2 STOPP drugs 1.26 (0.89-1.81). These results were based on complete data available from 1524 patients. In SENATOR Phase 2, a total of 828 adverse events which were adjudicated as probable or certain ADRs were identified among 380 of the 1537 randomized patients, i.e. ADR incidence of 24.7%. Applying ADRROP version 1 to SENATOR Phase 2 data, ADRs were still poorly predicted (AUC = 0.55). Using stepwise multiple regression analysis again, ADR risk coefficients were re-estimated in the new Phase 2 SENATOR data set. Based on these results, sex and impaired renal function (i.e. eGFR < 30 ml/min/1.73m²) were the most important predictors of ADRs. However, the predictive utility of the model was still limited, i.e. no better than ADRROP version 1. This could be expected, since the model is more flexible and thus responsive to Phase 2 data. When the ADR predictive power of this new model

was assessed, an AUC value of 0.58 was observed, i.e. poor ADR prediction once again. The logistic regression of the variables underlying the ADRROP indicators were applied to Phase 2 SENATOR data. All continuous variables were modelled with restricted cubic splines (with 5 degrees of freedom). The difference from the previous logistic regression model is that we used as much of the information in the covariates as possible, by avoiding the categorization of inherently continuous covariates, and allowing for some non-linearity. Nevertheless, the predictive utility of the model was still limited, with an AUC of 0.62 i.e. modest ADR prediction.

Summary & Conclusion

As with ADRROP version 1, ADRROP version 2 does not predict incident ADRs in multi-morbid older people with polypharmacy to a level that would be relevant in routine clinical practice. We conclude that a reliable ADR predictive tool does not emerge from multiple logistic regression analysis even when maximum flexibility is built into the ADR prediction model. The likely reason for this poor/modest level ADR prediction from both version 1 and version 2 of ADRROP is that the index patient population is too heterogeneous in terms of diagnoses, level of multi-morbidity and range of medications prescribed. We contend that this type of multifactorial model, originally based on the GerontoNet ADR risk scale (1) does not predict ADRs in older multi-morbid patients with polypharmacy to a level that would be clinically relevant. Even with a substantial and well defined prospective data set from SENATOR Phase 2, the level of ADR prediction observed with ADRROP version 2 is no better than with ADRROP version 1 (2). Accordingly, we suggest that a radically different approach to ADR predictive modelling in older people with multi-morbidity and polypharmacy is needed, such as ADR prediction with certain classes of medication and in certain diseases/clinical syndromes, rather than with polypharmacy in general.

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WP02 – Definition of Optimal Evidence-Based Non-Drug Therapies in Older People (ONTOP)

The ONTOP (Definition of Optimal Evidence-Based Non-drug Therapies in Older People) rationale is based on the fact that it is widely recognized that non-pharmacological (non-drug) therapies, i.e. exercise, physiotherapy, occupational therapy, speech & language therapy, nutritional therapy, psychological and behaviour therapy can be as or more effective than pharmacological (drug) therapy in the treatment of several common chronic conditions. Drug therapy and non-drug therapies are complementary in the management of older people with multi-morbidity. To date, however, there is no widely used compendium of non-pharmacological therapies for the common chronic medical conditions of late life. Therefore, they are underappreciated and underused in clinical practice. Consequently, the ONTOP work package aimed to fill this knowledge gap by undertaking a thorough literature search of systematic reviews that evaluated the efficacy of non-pharmacological treatments for 15 common medical conditions affecting older people in order to identify those treatments that are firmly evidence-based.

To reach this aim, ONTOP constituted a multidisciplinary group of geriatricians, clinical investigators, clinical epidemiologists, pharmacists and nurses. All of the ONTOP team members attended several workshops that were organized mainly in Ancona to understand and learn the methods of evidence retrieval as well as the application of the GRADE methodology in rating the evidence and formulating recommendations. In addition, several teleconferences were held to clarify and update issues related to methodology. During the entire duration of the project regular supervision of ongoing work was performed using both email and telephone.

The 15 clinical conditions chosen were the following ones: 1) Delirium, 2) Falls, 3) Pressure ulceration, 4) Urinary incontinence, 5) Dementia, 6) Heart failure, 7) Diabetes, 8) Sarcopenia/frailty, 9) Orthostatic hypotension, 10) Stroke, 11) Malnutrition, 12) Chronic obstructive pulmonary disease, 13) Vision impairment, 14) Hearing impairment, and 15) Osteoarthritis.

For each of these 15 conditions, the ONTOP group identified critical outcomes using the Delphi method for each of which developed reasonable clinical questions; prepared and launched search strategies into electronic databases (mainly Medline and the Cochrane Library and as necessary Embase, PsychINFO and CINAHL). From the relevant systematic reviews, the qualitative and quantitative data were retrieved to gather the evidence. Where necessary, meta-analyses were performed or updated as necessary. The evidence quality was then rated using the GRADE items—risk of bias, imprecision, inconsistency, indirectness and publication bias as follows: high, moderate, low or very-low. Based on the quality of evidence, the ONTOP group formulated recommendations in favour or against a non-pharmacological intervention to treat or prevent a critical outcome within any one of the 15 conditions. Usually strong recommendations were provided when a high (i.e., further research is very unlikely to change our confidence in the estimate of effect) or moderate (i.e., further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) level of evidence was present. Conversely, weak or conditional recommendations were provided in the presence of low (i.e., further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very-low (i.e., any estimate of effect is very uncertain) quality of evidence. In some circumstances, due to important uncertainty surrounding the evidence, no recommendations were provided.

A very large amount of work was undertaken in screening titles and abstracts, identifying the reviews and abstracting data from primary studies which required greater resources than those available within the grant finances. Therefore, when we requested the third amendment to the project, we proposed to reduce the number of conditions from 15 to ten. This request was formally accepted by the European Commission (see DOW SENATOR AMd003 of October 2016). However, we appreciated the importance to provide evidence based recommendations also for the five conditions that could not be evaluated with the original methodology, i.e. Diabetes, Osteoarthritis, Chronic obstructive pulmonary disease, Vision impairment and Hearing impairment. Therefore, we examined non-pharmacological interventions for these 5 conditions limiting the selection of the systematic reviews to those of highest quality, i.e. with AMSTAR score of ≥ 6 .

The recommendations were used to define in bullet-point format indications and contraindications of non-pharmacological therapies for which there is the strongest evidence base in each of the 15 chronic conditions. The original intention was that indications and contraindications would be included in the version of SENATOR software intended for market to provide advice to physicians not only on patients' drug therapy, but also on appropriate non-pharmacological interventions.

From the published literature, ONTOP succeeded in identifying 244 single or multicomponent non-pharmacological interventions for critical outcomes of the 15 conditions. In addition, ONTOP, based on strong recommendations, was able to formulate 37 indications to use non-pharmacological interventions to treat or prevent critical outcomes in 13 conditions

Delirium. Overall there were screened 3329 records retrieved from the medical literature from which 26 reviews were identified that allowed the identification of 31 primary studies. The outcomes rated as critical were delirium incidence for delirium prevention and delirium improvement and functional status for delirium treatment. Strong recommendations in favour of multicomponent interventions to prevent delirium, in surgical or medical wards, were formulated for high risk older patients. Strong recommendations *not* to use bright light therapy to prevent delirium in intensive care unit settings were provided.

Falls. Overall we screened 1460 records and assessed 108 full-text reviews to obtain 59 reviews of interest with an overall 159 primary studies. The outcome rated as critical was incident falls (encompassing fall rate and number of fallers). Strong recommendations were formulated in favour of exercise, Tai Chi, home safety assessment and

modification, and multifactorial interventions. Strong recommendations not to use knowledge/education alone was also formulated.

Pressure ulceration. After screening 675 records, we assessed 190 full-text reviews from which we identified 110 reviews of interested and obtained 65 primary studies for pressure ulcer prevention and 45 primary studies for pressure ulcer treatment. The outcome rated as critical for pressure ulcer prevention was incidence of new pressure ulcers whereas the outcome rated as critical for pressure ulcer treatment was rate of complete ulcer healing. Strong recommendations were formulated in favour of alternating pressure devices, regular repositioning, intra- and post-operative alternating pressure devices, and constant low pressure devices to reduce the incidence of new pressure ulcers. Strong recommendations were formulated in favour of pressure relieving device to heal pressure ulcers.

Urinary incontinence. After screening 2797 records, we evaluated 131 full-text reviews to obtain 33 relevant reviews and 25 primary studies. The outcomes rated as critical were frequency of episodes of urinary incontinence and quality of life. Strong recommendations were formulated in favor of group exercise therapy and multi-component behavioural therapy to minimize episodes of urinary incontinence.

Dementia. We screened 4392 records and assessed 84 full-text reviews to obtain 38 reviews with 142 primary studies. Behavioral and psychological symptoms in dementia was rated as a critical outcome. Strong recommendations were provided in favour of music therapy and behavioural management techniques in their different forms to treat behavioural disturbances.

Heart failure. We screened 1560 records and assessed 184 full-text reviews to obtain 91 reviews with 89 primary studies. Critical outcomes were all-cause mortality, all-cause hospital admission or re-hospitalization, quality of life and activities of daily living. Strong recommendations were formulated in favour of exercise-based cardiac rehabilitation to reduce all-cause hospitalizations; self-care management interventions management to reduce all-cause mortality and all-cause hospitalizations, and non-invasive tele-monitoring to decrease all-cause mortality.

Diabetes. We screened 6784 records and assessed 256 full-text reviews to obtain 50 reviews. For diabetes prevention, diabetes incidence was rated critical whereas for diabetes treatment the following outcome was rated critical for decision making: diabetic complications (ischemic heart disease, stroke, amputation, renal failure and eye disease), quality of life, glycosylated haemoglobin A1c (HbA1c), glycaemic control, and mortality. Strong recommendations were formulated in favour of diet and physical activity programs as well as Mediterranean diet supplemented with extra-virgin olive oil to reduce the incidence of diabetes in subjects at increased risk of type 2 diabetes, i.e. patients with impaired fasting glucose or with impaired glucose tolerance.

Sarcopenia and physical frailty. We screened 11665 records and assessed 130 full-text reviews to obtained 10 reviews. From these we identified 139 primary studies that provided 6 studies for inclusion. The outcomes rated as critical were muscle strength, physical performance muscle function, muscle mass and muscle function, activities of daily living, and falls. Strong recommendations were formulated in favour of exercise (including resistance training) for sarcopenia and multidisciplinary intervention for frailty in order to improve physical performance.

Stroke. We screened 13,627 records and assessed 357 full-text reviews to obtain 210 reviews and 83 primary studies. Critical outcomes were physical function, quality of life and disability. Since it is well established that patients with stroke admitted to a specialist stroke unit and undergoing rehabilitation have improved outcomes, including reduced disability and death, these two interventions were not included in the systematic search. No strong recommendations were provided in favour of any of the non-pharmacological interventions investigated.

Chronic obstructive pulmonary disease. We screened 2930 records and evaluated 186 full-text reviews to obtain 40 reviews for inclusion. Outcomes rates as critical were dyspnoea, exacerbations, and health related quality of life. Strong recommendation in favour of pulmonary rehabilitation to improve dyspnoea and self- management intervention to improve health-related quality of life.

Hearing impairment. We screened 1244 records and assessed 28 full-text reviews for eligibility obtaining three systematic reviews for inclusion. Outcomes rated as critical were improved hearing acuity, quality of life and cognitive impairment. Strong recommendations were formulated in favour of hearing aids for mild to moderate hearing loss.

Osteoarthritis. We screened 2244 references and assessed 38 systematic reviews (SRs). Outcomes rated as critical were pain reduction, physical function improvement and QoL improvement. We provided strong recommendations in favour of specific hand exercises, manual therapy and multimodal intervention (combining joint protection, local heat, and hand exercises) to reduce pain in older patients with symptomatic hand OA. Strong recommendations were also provided in favour of general physical exercise interventions (aerobic/resistance) to reduce pain and improve function in older patients with symptomatic knee OA. A weak recommendation was provided in favour of other physical exercise interventions (aquatic exercise, whole body vibration platform, Tai Chi) to reduce pain and improve function in older patients with symptomatic knee OA. We provided strong recommendations in favour of land based (as distinct from water-based) exercises to reduce short-term pain and improve physical function in older patients with symptomatic hip osteoarthritis. For combined hip and knee OA, we provided strong recommendations in favour of physical exercise (strength training, flexibility, and aerobic exercise, Tai Chi and Badwajin) to improve physical function in older people.

Given the lack of high or moderate quality of evidence we could not to provide any practical recommendations in favour of or against the use of non-pharmacological interventions for orthostatic hypertension, malnutrition and vision impairment. Concerning visual impairment, it is important to specify that, since it is well established that cataract surgery improves vision acuity in older patients, this intervention was not included in the systematic search.

The ONTOP work package has produced the largest compendium of evidence based indications and contraindications to non-pharmacological therapies in older subjects that will be useful to all physicians treating older patients.

WP03 – Data Collection on European Drug Availability, Pricing & Policies.

Introduction

In the SENATOR project, it was necessary to build a Drug File that was comprehensive enough to include all available prescription and non-prescription medications in the 6 participating countries. This was in order to capture every medication that could be involved in STOPP and START criteria, as well as all potentially serious drug-drug and drug-disease interactions covered by the SafeScript® database. Without an up-to-date and comprehensive Drug File, there was the real possibility that SENATOR software would fail to highlight potentially serious and important adverse pharmacotherapy and thereby fail to protect the multi-morbid older patient exposed to polypharmacy. No comprehensive Drug File that contained all medications that were available in all 6 countries was commercially available. With these considerations in mind, the SENATOR consortium set about creating the Drug File from existing accessible drug databases and thereafter validating the Drug File to ensure its accuracy and comprehensiveness.

Methods

The Drug File was defined as that directory of medications that was available in each of the 6 participating clinical sites. Thus, the locally available directories of available medications were combined into a single overarching Drug File. Initially, this work was led by Southern Denmark University (SDU), but later transferred to UCC when SDU left the project. The final Drug File eventually included over 61,000 medications. All Drug File medications were identified by ATC (Anatomical Therapeutic Chemical) codes which were checked for accuracy.

The next task was to link all of the Drug File medications by means of their verified ATC codes to ICD-10 disease codes and to validate all such linkages. This was deemed essential for the proper working of the SENATOR software, since the correct identification of certain drugs in the presence of certain medications in individual patients was needed in order to trigger particular STOPP and START criteria/rules. Correct drug/disease code linkage also underpins the correct identification of potentially serious adverse drug-drug and drug-disease interactions. However, the latter interactions were available through commercially available databases such as SafeScript®.

However, SafeScript® was not the locally used database for identifying adverse drug-drug and drug-disease interactions in some centres. Where that was the case, we used those alternative databases that were available alongside the STOPP and START criteria that were activated by SENATOR software. The combination of SENATOR-generated STOPP and START criteria in combination with the details of adverse drug-drug and drug-disease interactions formed the essential details contained in the locally generated SENATOR advice reports.

Results

The Drug File was successfully constructed and validated for use in all 6 clinical sites i.e. the Drug File was capable of recognizing all available medications in all sites and converting them to ATC codes which, when linked to STOPP and START criteria or to drug-drug and drug-disease constraints, successfully and appropriately created a potential medication hazard warning to the prescriber. Once the Drug File had been fully validated for all sites, it was provided to the Clanwilliam Health® team who provided the functional software interface between SENATOR and the Drug File.

WP04 – Design & Construction of SENATOR

Introduction

In the absence of any commercially available or fully elaborated software version of STOPP/START criteria, it was clear that a new, bespoke software method of deploying STOPP/START would be an essential part of the SENATOR project. For this reason, the project engaged the collaboration of an established healthcare software company i.e. Helix Health® which later became part of Clanwilliam Health®. The requirement was to design and build a software that could generate appropriate customized pharmacotherapy advice reports aimed at optimizing multi-morbid patients' pharmacotherapy. Such bespoke advice reports which would then become the intervention for the SENATOR trial.

Methods

Software design personnel worked closely with the project co-ordinating team at UCC in scoping the design of the software. The expressed aims of the UCC clinicians were to have a user-friendly efficient software that was capable of extracting the necessary data from the electronic Case Report Form (eCRF) with which to identify drugs which are not indicated, potentially inappropriate medications (STOPP criteria, version 2), potential prescribing omissions (START criteria, version 2), drug-drug interactions and drug-disease interactions. In the initial list of medication assessment components were (i) an assessment of ADR Risk in Older Persons (ADRRPOP) tool, (ii) an assessment of appropriateness of palliative pharmacotherapy, (iii) a translation tool for conversion of all drug brand names to generic names, (iv) an assessment of overall medication appropriateness (Medication Appropriateness Index) and (v) a list of appropriate complementary non-drug therapies appropriate to an individual patient's list of chronic medical conditions.

Results

Extensive design work and examination of the challenges with providing a working interface between SENATOR software and the eCRF and the Drug File, as well as examination of the data provided from the observation Phase 1 of the SENATOR trial (c.f. WP08) led to a rationalization of the SENATOR software design in order to retain the essential components that had a direct impact on the SENATOR trial endpoints. These components were: (i) Drug indications, (ii) STOPP criteria, (iii) START criteria, (iv) Drug-drug interactions, (v) Drug-disease interactions and (vi) ONTOP delirium prevention in at-risk patients. Once SENATOR software had deployed this list of prescribing constraints, an advice report was generated through the eCRF, ready for delivery to the attending clinician of the particular patient in question.

WP05 – Pilot Testing & Scientific Validation of SENATOR

Introduction

The intentions of SENATOR software are (i) to interrogate the input-data provided by an electronic Case Report Form comprising patient-specific demographic, functional, medical, laboratory and pharmaceutical variables, and (ii) to generate an individualized report containing explicit recommendations to optimize that patient's prescription. Conduct of WP05 was contingent on successful completion of the following SENATOR work packages:

- (i) **WP01:** The development and validation of Adverse Drug Reaction Risk in Older People (ADRROP) tool.
- (ii) **WP03:** The development of a comprehensive drug repository containing information about drug availability and pricing in the 6 European countries participating in the SENATOR project.
- (iii) **WP04:** The development of the SENATOR software by Clanwilliam Healthcare® (previously Helix Health®) with medical input and support from the co-ordinating centre in University College Cork.
- (iv) **WP10:** The development and validation of the SENATOR electronic Case Report Form (eCRF).

Aims of WP05

- (i) to pilot test and scientifically validate the SENATOR software in terms of its ability to interrogate input data from the eCRF (WP10) and to generate an output containing specific prescribing recommendations for hospitalized older people with multi-morbidity.
- (ii) to complete any necessary modifications to the prototype SENATOR software prior to translation and language validation of SENATOR (WP06) and the randomized controlled trial using SENATOR software as an intervention (WP08).

Methods

The testing and scientific validation of the prototype SENATOR software was completed in English. Essential tasks were performed in a step-wise fashion as follows:

- (i) Review and modification of the SENATOR output report to reflect achievable and clinically meaningful prescribing recommendations.
- (ii) Pre-validation of the prototype SENATOR software comprising detailed testing, modification (where necessary) and re-testing of every potential SENATOR-generated prescribing recommendation (3 pre-validation rounds).
- (iii) Development of 20 comprehensive clinical test cases of older adults with multi-morbidity and multiple medications. Detailed assessment of these 20 clinical test cases by two expert assessors (PG, AL) to determine a "GOLD standard" clinical measure of prescribing appropriateness with relevant recommendations.
- (iv) Transcription of the 20 clinical test cases into the eCRF, subsequent interrogation by the SENATOR software prototype and comparison of the SENATOR output with the Gold Standard assessment.
- (v) Assessment of the 20 clinical test cases by clinical practitioners who were trained in geriatric pharmacotherapy (2 physicians and 2 pharmacists) to determine clinical inter-rater reliability.
- (vi) Comparison of manual clinical recommendations of trained clinical practitioners (as in item (v) above) to that of the Gold Standard assessment and that of SENATOR-generated recommendations.

Results

The inter-rater agreement between Gold Standard (GS) expert assessment of potentially inappropriate prescriptions and SENATOR electronic software recommendations was tested in three rounds following necessary modification of the coding of specific STOPP/START criteria. The co-efficient of agreement increased progressively with each modification and showed very good inter-rater reliability between Gold standard expert prescribing recommendations and SENATOR software recommendations (see **Table 1**).

Table 1: Level of agreement (kappa co-efficient) between gold standard and SENATOR

Gold Standard versus SENATOR software recommendations	Round 1	Round 2	Round 3
All criteria included from GS output; Criterion STOPP A1 excluded from SENATOR output	0.698	0.76	0.78
Criterion STOPP A1 excluded from GS output; Criterion STOPP A1 excluded from SENATOR output	0.72	0.79	0.80
Criterion STOPP A1, START I1 and I2 excluded from GS output;			

Criterion STOPP A1, START I1 and I2 excluded from SENATOR output	0.77	0.86	0.87
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The Inter-rater reliability of prescribing recommendations between Gold Standard expert assessment and that of Clinical Practitioners (2 physicians and 2 clinical pharmacists) was also evaluated, using the same clinical cases as above. The levels of agreement ranged from 0.58 (moderate) to 0.67 (good). This analysis of everyday clinical assessment was evaluated with the comparator statistics between the Gold Standard and the SENATOR software. **The results demonstrate that the agreement between the Gold Standard and SENATOR software (K = 0.87) is stronger than that between everyday clinical practitioners and the Gold Standard (K = 0.58 to 0.67).**

DISCUSSION

The UCC team worked very closely with the SENATOR software development team and eCRF development team (ClinInfo®) to ensure efficient but high yield data input processes that were necessary for the extensive electronic coding of the SENATOR software.

The validation process shows that the final version of the SENATOR software prototype was reliable in determining potentially inappropriate medications and potential prescribing omissions according to STOPP and START criteria respectively. SENATOR's inter-reliability with an expert Gold Standard clinical assessment was very good (kappa value > 0.8) i.e. the software identified the relevant STOPP/START recommendations more accurately than practicing clinicians using a paper-based system.

The ongoing accurate functioning of the SENATOR software was dependent on careful and precise data input from the primary researchers across the 6 trial sites. Prior to trial commencement all primary researchers had training in WHO ICD-10 coding and in the correct and precise completion of the eCRF. Throughout the SENATOR intervention study, the primary researchers were required to check each report for its accuracy so that if any subsequent concerns arise, they can be addressed quickly and efficiently. No significant adverse event with the software was reported during the study.

WP06 – Translation & Language Validation of SENATOR

The objectives of work package 6 are all accomplished. In addition to the translation of the START/STOPP criteria, the drug-drug interactions, drug-disease interactions and ONTOP recommendations have been successfully translated from English into the four other clinical site languages (i.e. Dutch, Icelandic, Italian, and Spanish) with assistance of SERMAS, INRCA and LUH.

Table 2: Overview of the translation status of each of these aspects to date.

	Translation method	Original Text	Translation into Target Languages			
		Available in English	Dutch	Icelandic	Italian	Spanish
START criteria	Forward & backward	✓	✓	✓	✓	✓
STOPP criteria	Forward & backward	✓	✓	✓	✓	✓
Drug-drug interactions	Forward only	✓	✓	✓	✓	✓
Drug-disease interactions	Forward only	✓	✓	✓	✓	✓
ONTOP recommend.	Forward & backward	✓	✓	✓	✓	✓

After finalization of this work package in 2015, small practical inaccuracies correlated with translation emerged in the SENATOR report. Therefore each trial site had to perform a check-up of the report in the corresponding language, to make sure that the final report didn't contain any linguistic imperfections. Also, the ICD-10 coding was translated from English into the four other clinical site languages. Consequently, the potential drug-drug interactions, drug-disease interactions are mentioned in the corresponding language instead of English in the report meant for the treating physician, to enhance the credibility of the report and to make sure that every non-English speaking physician can fully understand the report.

The relevance of the translation work performed within the SENATOR trial lies in the fact that the already widely used STOPP/START criteria are now available also in other four European languages other than English, i.e. Dutch, Icelandic, Italian and Spanish. This will facilitate not only research initiatives in the field of geriatric pharmacotherapy and appropriate prescribing in the related countries but also simplify the use and application of these criteria in daily clinical practice by different healthcare providers.

WP07 – Trial Organisation and Governance

WP07 involved developing and implementing effective guidance documents and management structures to ensure all aspects of the clinical trial, from initiation to close down, were conducted to a high standard that was consistent across all sites and in line with ICH Good Clinical Practice, ensuring the safety of patients involved and the integrity of the data collected.

Primarily the Trial Coordination Centre (TCC) was formed with the responsibility of achieving these objectives. The TCC was chaired by the Project Coordinator, Professor Denis O'Mahony and key staff employed included a Clinical Trial Coordinator, a Data Manager, a Trial Monitor, a Trial Statistician and an End Point Liaison Officer. The TCC undertook the following key responsibilities: (i) developing all study documentation versions controlling any modifications, (ii) ensuring research staff completed the necessary training, (iii) maintaining the Trial Master File, (iv) monitoring trial conduct and progress and (v) reporting to/facilitating interaction between sites and other stakeholders within the project including the Clanwilliam Group, Clininfo, Ethics and Safety Group (ESRG), Scientific Advisory Board (SAB) and Sponsor representatives. A key role of the TCC was to coordinate the adjudication of all end points reported in the trial. This task was undertaken by the End Point Liaison Officer who trained the Potential End Point Adjudication Committee (PEPAC) members, ensured compliance with the trial protocol and monitored progress against agreed milestones. The TCC met fortnightly to monitor progress and also hosted monthly teleconferences for Primary Researchers providing a forum to address any questions on technical or practical issues experienced by the research staff and for the TCC to assess if there were any further training needs/additional support required.

The Trial Protocol described the objectives, design, methodology, statistical considerations and organization of the clinical trial, and was approved by the ESRG, SAB and local ethics committees prior to implementation. A Manual of Operations, aimed at primary researchers, complemented the clinical trial protocol and provided detailed, more specific guidelines for the day to day running of the trial. These guidelines covered all aspects of trial conduct from patient screening, consent and randomization to delivering the intervention, data collection and patient safety. A CRF Completion Guidelines document provided instruction for completing every data field on the electronic CRF to eliminate potential for ambiguity when answering the questions, ensuring consistency in data collection across all six recruiting sites. An SOP specifically outlining how to report Prevalent and Incident Adverse Events (SOP 01) defined prevalent and incident adverse events, outlined which events to report and when to assess and report the events. A training tool was written in Powerpoint® format and SENATOR Training Slides, summarizing the trial protocol and guidance documents were produced. These were an essential aid for the Trial Coordinating Centre to ensure each primary researcher was adequately trained prior to working on the trial. A Clinician Information Sheet, compiled for clinicians, explained what was required from them when a patient of theirs was randomized to the SENATOR arm of the trial. A Trial Close-Out SOP described the responsibilities and procedures for the close-out of the trial and ensured all tasks were completed within the required timeframes.

To safeguard the appropriate ethical and high-quality conduct of the study, a Trial Monitoring Plan was developed and approved by the SENATOR ESRG, Steering Committee and Sponsor representative prior to implementation. The Trial Monitor hosted initiation meetings remotely (by Skype®) to ensure all essential documentation was present and all required training was completed prior to opening the site for patient recruitment. Central Monitoring of the trial data was undertaken by the TC and, furthermore, each site received two on-site monitoring visits, conducted by the Trial Monitor during which the Investigator Site Files were reviewed for completeness, source data were verified and compliance with the trial protocol, SOPs and the Manual of Operations were checked in detail. Any local issues with trial organization or conduct were discussed assigning appropriate Corrective and Preventative Actions were necessary. All monitoring reports were sent to the ESRG and SAB for review.

The TCC developed the Patient Information/Informed Consent documentation, which was approved by the ESRG and Cork ethics committee. The documentation was then translated and individualized to the local sites and underwent a quality check by the trial Sponsor representative before being submitted for approval to the various local ethics committees. The TCC outlined informed consent procedures, provided training and, during monitoring visits, ensured informed consent procedures were in line with SENATOR guidance, local ethical approval and ICH Good Clinical Practice.

WP07 was central to ensuring the clinical trial was conducted to a high standard achieving high quality data whilst ensuring patient safety. It developed and implemented functional organizational structures and trial management procedures that will serve as a successful template for future trials.

WP08 – Randomized Controlled Trial of SENATOR vs. ‘Standard Care’

Phase 2 of the SENATOR trial (randomization phase) got under way in July 2016 at the coordinating centre in Cork. Recruitment in the other 5 sites was initiated over the next 3 months. Recruitment was started in sequence rather than in tandem for a number of reasons, including the need to carry out site initiation visits by the trial monitor, completion of summer leave by primary researchers and finalization of local ethical committee approval. In total, 1537 patients were enrolled across the 6 clinical sites (765 control patients, 772 SENATOR intervention patients). The sample characteristics of the two cohorts are illustrated in Table 3. Highest education attainment is an accepted surrogate marker of socioeconomic status. As shown in Table 3, a higher proportion of SENATOR active intervention arm patients completed second level (high school) education than control patients (31.7% vs. 26.5%). However, this difference was counterbalanced by a higher proportion of control patients completing third level (university) education than SENATOR active intervention patients (12.0% vs. 8.2%). Per the protocol, patients in the control arm received standard pharmaceutical care as it existed in each site at the time of randomization.

Patients in the intervention arm received standard pharmaceutical care plus SENATOR-guided medication optimization adjustment as accepted and implemented by their attending clinicians. The SENATOR advice report was generated within 60 hours of admission and immediately transmitted electronically to the senior attending clinician. In addition, a copy of the advice report was placed in the intervention patients’ case records in order to further attract the attention of the attending medical staff. The attending medical staff then applied their own clinical judgment as to how much or how little of the SENATOR advice report they deemed applicable in each patient’s case. Any adjustments to the intervention arm patients’ pharmacotherapy were made by the attending medical staff as per the trial protocol.

Table 3: Sample characteristics according to SENATOR Phase 2 randomization arm.

Variable	N	Total (n = 1537)	Control (n = 765)	SENATOR (n = 772)	Test p-value
Site	1537				1
<i>Cork</i>		405 (26.4%)	201 (26.3%)	204 (26.4%)	
<i>Reykjavik</i>		295 (19.2%)	147 (19.2%)	148 (19.2%)	
<i>Aberdeen</i>		285 (18.5%)	141 (18.4%)	144 (18.7%)	
<i>Madrid</i>		190 (12.4%)	95 (12.4%)	95 (12.3%)	
<i>Ghent</i>		205 (13.3%)	102 (13.3%)	103 (13.3%)	
<i>Ancona</i>		157 (10.2%)	79 (10.3%)	78 (10.1%)	
Sex	1537				0.81
<i>Female</i>		725 (47.2%)	358 (46.8%)	367 (47.5%)	

	<i>Male</i>		812 (52.8%)	407 (53.2%)	405 (52.5%)	
Age (years)		1537	78 [72, 84]	78 [72, 84]	78 [72, 84]	0.26
Education		1537				0.05
	<i>No schooling</i>		37 (2.4%)	16 (2.1%)	21 (2.7%)	
	<i>Primary school education only</i>		561 (36.5%)	283 (37%)	278 (36%)	
	<i>Some secondary education</i>		281 (18.3%)	146 (19.1%)	135 (17.5%)	
	<i>Complete secondary education</i>		448 (29.1%)	203 (26.5%)	245 (31.7%)	
	<i>Some third level education</i>		55 (3.6%)	25 (3.3%)	30 (3.9%)	
	<i>Complete third level education</i>		155 (10.1%)	92 (12%)	63 (8.2%)	
Smoker		1537				0.8
	<i>Yes</i>		108 (7%)	52 (6.8%)	56 (7.3%)	
	<i>No</i>		1429 (93%)	713 (93.2%)	716 (92.7%)	
Alcohol		1537				0.53
	<i>Yes</i>		432 (28.1%)	209 (27.3%)	223 (28.9%)	
	<i>No</i>		1105 (71.9%)	556 (72.7%)	549 (71.1%)	
Domestic help		1515				1
	<i>Yes</i>		604 (39.9%)	302 (39.9%)	302 (39.8%)	
	<i>No</i>		911 (60.1%)	455 (60.1%)	456 (60.2%)	
Personal care		1515				0.96
	<i>Yes</i>		384 (25.3%)	191 (25.2%)	193 (25.5%)	
	<i>No</i>		1131 (74.7%)	566 (74.8%)	565 (74.5%)	
CIRSG		1537	15 [11, 19]	15 [11, 19]	15 [11, 19]	0.91
Previous fall		1537				0.54
	<i>Yes</i>		570 (37.1%)	290 (37.9%)	280 (36.3%)	
	<i>No</i>		967 (62.9%)	475 (62.1%)	492 (63.7%)	
Previous ADR		1537				0.57
	<i>Yes</i>		669 (43.5%)	327 (42.7%)	342 (44.3%)	
	<i>No</i>		868 (56.5%)	438 (57.3%)	430 (55.7%)	
Barthel		1537	18 [14, 20]	18 [14, 20]	18 [14, 20]	0.92
Number of medications		1537	10 [8, 13]	10 [8, 13]	10 [8, 13]	0.4

SENATOR Phase 2 results

As defined in the protocol, the Primary Endpoint was the proportion of patients with at least one adjudicated probable or certain, non-trivial hospital-acquired ADR occurring within 14 days of enrolment during the index hospitalization. There were 475 of these in total, which were experienced by 379 patients. This was a total event rate of 24.66%.

Protocol defined Secondary Endpoints were as follows:

S1 - The proportion of patients with at least one adjudicated possible, probable or certain, non-trivial hospital-acquired ADR occurring within 14 days of enrolment during index hospitalization.

S2 - The proportion of patients with at least one adjudicated probable or certain, non-trivial hospital-acquired, pre-specified ADR occurring within 14 days of enrolment during index hospitalization.

SPC - The number of adjudicated probable or certain, non-trivial hospital-acquired ADRs occurring within 14 days of enrolment during the index hospitalization (i.e. the count of Primary Endpoint events).

S1C - The number of adjudicated possible, probable or certain, non-trivial hospital-acquired ADR occurring within 14 days of enrolment during index hospitalization (i.e. the count of S1 events).

S2C - The number of adjudicated possible, probable or certain non-trivial hospital-acquired, pre-specified ADRs per patient, occurring within 14 days of enrolment during the index hospitalization (i.e. the count of S2 events).

The tertiary endpoint results are described in detail in the WP11 summary below. Mortality at 12 weeks was another tertiary endpoint. In the control group, 51 of the 720 patients had died at 12 weeks from randomization (7.62%); in the SENATOR group, 54 of the 729 patients (8.0%) had died, this was not significant ($p=0.82$).

Pre-specified ADRs are those 12 adverse events included in the Trigger List, as described in the trial protocol. A 13th adverse event, labelled "Unspecified", was added to capture other common, predictable ADRs that may not be detected by the other events were not included on the Trigger List. For example, if a patient with a history of penicillin allergy develops a severe acute skin rash following inadvertent exposure to a penicillin, the "Unspecified" clinical event criterion in the Trigger List was triggered and would capture such an ADR accordingly. Similarly, other well-known ADRs following exposure to recognized culprit drugs would be identified through the "Unspecified" adverse event in the Trigger List. The distributions for each endpoint, as well as crude tests of differences between study arms, are given in Table 4 below. Based on these simple tests, there was no evidence for a difference between study arms for any endpoint.

Table 4: The distributions for each endpoint, as well as crude tests of differences between study arms.

Variable	N	Total (n = 1537)	Control (n = 765)	SENATOR (n = 772)	Test p-value
Primary	1537				0.92
No		1158 (75.3%)	575 (75.2%)	583 (75.5%)	
Yes		379 (24.7%)	190 (24.8%)	189 (24.5%)	
S1	1537				0.23
No		996 (64.8%)	484 (63.3%)	512 (66.3%)	
Yes		541 (35.2%)	281 (36.7%)	260 (33.7%)	
S2	1537				0.48
No		1198 (77.9%)	590 (77.1%)	608 (78.8%)	
Yes		339 (22.1%)	175 (22.9%)	164 (21.2%)	

SPC	1537	0 [0, 0] (0 to 4)	0 [0, 0] (0 to 4)	0 [0, 0] (0 to 4)	0.74
S1C	1537	0 [0, 1] (0 to 6)	0 [0, 1] (0 to 5)	0 [0, 1] (0 to 6)	0.17
S2C	1537	0 [0, 0] (0 to 4)	0 [0, 0] (0 to 4)	0 [0, 0] (0 to 3)	0.41

Note: Test p-values are from Chi-squared tests for Primary, S1, and S2; and Kruskal-Wallis tests for SPC, S1C, and S2C.

SENATOR report advice adherence

The level of adherence among attending clinicians with advice points in the SENATOR reports issued relating to patients in the intervention arm had a crucially important influence on the endpoint analysis and the overall outcome of the SENATOR trial. The levels of adherence across the 6 participating sites was similar. Overall adherence with SENATOR advice points was approximately 15% and was observed consistently at this level in all clinical sites.

Summary & Conclusions

In summary, we randomized 1537 patients in Phase 2 (randomization phase) of SENATOR; 765 patients to the control arm (standard pharmaceutical care) and 772 patients to the intervention arm (standard pharmaceutical care plus SENATOR advice report to attending medical staff once within 60 hours of admission). The primary endpoint, incident probable or certain ADRs occurring within 14 days of randomization, was not statistically different in the control arm (24.8%) compared to the intervention arm (24.5%). Similarly, none of the secondary endpoints showed a statistically significant difference between the control arm and the intervention arm.

Importantly, the level of adherence by attending medical staff in the intervention arm with SENATOR medication advice points was relatively low at 15%. This low level of adherence suggests that the provision of unsolicited SENATOR reports in the current European clinical environment is not by itself effective at reducing ADRs. Nevertheless, it must be noted that primary researchers applied the intervention using their clinical judgment as per the final study protocol (c.f. Protocol page 22). Attending senior medical staff were alerted to their patients being allocated to the intervention arm, a copy of the bespoke SENATOR advice report pertaining to each intervention patient was sent by email to the patient's attending specialist, and a copy of the SENATOR advice report was also entered to the patient's medical records.

We conclude the following:

- (i) We successfully constructed and validate a software engine that deploys STOPP and START criteria, identifies potentially serious drug-drug interactions, drug-disease interactions, as well as potentially beneficial non-drug therapy (the latter as a proof-of-concept). SENATOR software worked efficiently in terms of producing swift and accurate treatment advice relevant to individual older patients with multi-morbidity and polypharmacy.
- (ii) However, provision of SENATOR software-generated medication advice reports to the clinicians attending older patients with multi-morbidity and associated polypharmacy is in itself insufficient for the purpose of attenuating incident ADRs in this high-risk patient population.
- (iii) Additional research is required to address the hypothesis as to whether a modified intervention with enhanced adherence with SENATOR software-generated medication advice reports will have a significant impact on incident ADRs.

Future Directions

It is likely that a different system is required in most busy general hospitals in Europe for software-driven careful medication review of older patients with multi-morbidity and associated polypharmacy. We contend that to achieve maximum benefit from software engines such as SENATOR, provision of sufficient numbers of well-trained clinical pharmacists within the general hospital will be necessary. Pharmacists specially trained in geriatric pharmacotherapy would take on the responsibility of medication review and application of STOPP/START criteria as well as detection of potentially serious drug-drug and drug-disease interactions. They would also have a remit to further discuss proposed changes of medication with attending senior medical staff in a routine, systematic manner that maximizes the adherence of prescribers with pharmacotherapy advice points that are agreed to be relevant and clinically important. All of this work should, in the view of the SENATOR consortium, be undertaken under the supervision of specialists in Geriatric Medicine for maximum impact and maximum safety.

WP09 – Ethics & Safety Monitoring

WP9 comprised the responsibility for safety monitoring, ensured high research standard of research and the protection of participants' rights and welfare.

Two essential committees were established under WP9.

(i) An independent four member Ethics and Safety Review Group (ESRG). The ESRG members have combined expertise in research ethics, geriatric medicine and pharmacotherapy. The ESRG met annually to review the trial metrics concerning study recruitment, follow-up, ADR ascertainment, patient safety and reporting of adverse events. The ESRG approved the trial informed consent procedures, the trial risk registry (set up and maintained at the Trial Coordinating Centre) and reviewed all monitoring reports for the individual study sites. Any potential deleterious event or potential harm accruing to a patient as a consequence of study participation was recorded on a trial deleterious event form by the clinical site teams and sent to the Trial Coordinating Centre. The trial deleterious events were assessed by the ESRG in real time. The ESRG completed a trial safety review of the un-blinded ADR event rates between the two randomized trial arms. In this context, the ESRG considered a report from an independent statistician and concurred with the statistician's conclusion that there no significant difference in adverse events between the two groups in SENATOR.

(ii) An independent seven member Scientific Advisory Board (SAB) was established under WP09 to ensure a high standard of research and review the overall trial progress. The Scientific Advisory Board members are senior academic clinicians, including five geriatricians, one clinical pharmacist and one pharmacist. The Scientific Advisory Board remained active throughout the project by attending GA meetings, STC meetings and held regular teleconferences.

The submission of the ethical applications was managed and overseen centrally by the Trial Co-ordinating Centre, based in the Clinical Research Facility, Cork. All patient-related documents, such as SENATOR trial information leaflets and trial participation consent forms were translated by Site Investigators and modified as needed to meet local ethical committee requirements.

Over the course of Phase 1 and Phase 2 of the SENATOR clinical trial, there were no major patient safety threats encountered. Any serious adverse patient events (including death) were reported and reviewed by the ESRG and following assessment, the ESRG reported back to the Trial Co-ordinating Centre, the local clinical site where the adverse event had occurred and to the SAB. No adverse event reported to the ESRG was deemed attributable to the SENATOR software intervention or from participation in the SENATOR trial. The SAB maintained ongoing oversight on all scientific aspects of the project throughout the life of SENATOR. All important documents including periodic reports and final trial protocol were reviewed by the SAB and feedback was invited and advice points were provided by the SAB to the consortium. Formal face-to-face review and feedback from the SAB to the consortium was an integral part of each GA meeting.

During the SENATOR trial, a Trial Monitor based at the Trial Coordinating Centre in Cork visited each of the 6 clinical sites to ensure that primary researchers were operating and completing the eCRF fully and appropriately and that all aspects of the Standard Operating Procedures relating to the SENATOR trial were being

implemented in an efficient, safe and appropriate manner. Trial Monitor reports following each site visit were provided to the project Co-ordinator, to ESRG members and to the trial monitoring staff based at UCC, as well as to the local site co-Principal Investigator. All issues identified by the Trial Monitor were resolved fully and speedily and outcomes reported to the ESRG.

WP10 – Data Management

Background

The management of all SENATOR project data generated through the eCRF was the shared responsibility of the project co-ordination centre at UCC and ClinInfo®, the SME with responsibility for all matters relating to the eCRF. The eCRF was, by necessity, a complex design because of the large number of data points arising from the patients' list of demographic details, medical conditions, the various medications used to treat those conditions, laboratory test result data, clinical status data (incorporating physical function and cognitive function) and healthcare utilization data. The eCRF and SENATOR software interface was complex because it had to incorporate the Drug File (based on ATC codes), ICD-10 disease codes as well as Drug-Drug Interaction and Drug-Disease Interaction databases. Furthermore, SENATOR software deployed STOPP and START criteria as the main method of detection of potentially inappropriate medications (STOPP) and potential prescribing omissions (START). Once all of the software interface platforms were functioning satisfactorily and validated as outlined in the WP05 summary above, the task of receiving and storing all SENATOR trial data began. The Trial Co-ordination Centre staff at UCC worked closely with the ClinInfo® staff to ensure all data were stored to a sufficiently high standard of organization and security. ClinInfo® had customizable access control with each user being assigned a user code, password and a user role containing a number of permissions.

A customizable password policy in the System Management module enables restrictions and requirements to be set on password creation. In addition to the US hosting facility ClinInfo® has a mature facility based in Lyon, France. All services are accessible through internet by a secure internet connection (https). The servers are located in protected premises, with remote control surveillance of local alarms. Additional security is achieved with strict physical security policy hardware firewall, frequent password changes and separation of test and development machines from the production system. ClinInfo® makes daily complete backups of the Oracle® database and all other systems. Oracle® log files (which allow recovery of all modified data in case of a possible crash) are duplicated and located on separate disks. A comprehensive data management plan was developed which outlined all procedures and plans for the data life cycle of the study. This was developed by the Data management department staff at the CRF-C in UCC.

All paper documents relating to SENATOR will be stored for the requisite 15 years in each of the clinical sites and partner premises following the end of the project i.e. until 30th June 2033. Project Master File documents will be stored by the Trial Co-ordination Centre staff at UCC for the same period.

Data Analysis

The task of data analysis lay primarily with the Trial Co-ordination Centre staff at UCC. A senior UCC statistician in collaboration with the WP08 leader and the project coordinator took prime responsibility for the data analysis. As per protocol, the data analysis plan was adhered to fully. Phase 1 data were analyzed following data cleaning and a statistical report was produced which later formed the basis of a full scientific publication (Lavan A et al. *Ther Adv Drug Saf* 2018 Jan;9(1):13-23.). Following the enrolment of the last patient in Phase 2 of SENATOR, data cleaning for Phase 2 was carried out over a 2 month period. The Phase 2 data were then analyzed statistically as per the statistical analysis plan. Primary and secondary endpoint data were subsequently reported to the SENATOR consortium at the final GA meeting in Cork on May 7-9, 2018. Further data analysis was undertaken on completion of all 12 week follow-up data collection. The latter was a shared task between University of East Anglia and Trial Co-ordination Centre staff at UCC, given the emphasis on quality of life and economic impact of SENATOR among the tertiary endpoints of Phase 2.

Data Storage

As with all multi-centre clinical trials, there is a requirement within SENATOR to store all locked-down data securely for at least 15 years from the end of the SENATOR project i.e. until June 2033. This responsibility has been taken up by the Trial Co-ordination Centre staff at UCC. The trial database meets all European personal data storage statutory requirements and is fully compliant with recently enacted GDPR regulations. Provision of direct access

to data collected in the 6 participating clinical centres will be granted at 12 months from the lock-down of the SENATOR database i.e. in mid-2019.

Data Publication

As with all large-scale projects, the SENATOR consortium has a Publications Committee which includes the Co-Principle Investigators, the trial statistician and the WP leaders. As per Publications Committee policy, the SENATOR Publications Committee will endeavor to publish all SENATOR project data that are of sufficient quality, originality and importance in a timely fashion in peer-reviewed scientific journals, preferably with open access provided in order to maximize the reach of the project. The SENATOR Publications Committee has also agreed that, where appropriate, the SENATOR data may be utilized to provide useful and important information about various aspects of medication use in multi-morbid older people that are relevant to other research projects. The latter is, however, subject to ethical committee approval as per normal practice relating to databases containing patient data and other information.

Where appropriate i.e. deemed sufficiently relevant to the wider public in Europe and/or participating countries within SENATOR, project database information will be provided to the public media in a suitable format. This approach to dissemination will be taken where, in the judgment of the Publications Committee, it is in the public interest to provide such information and will be carried out in a timely manner. The SENATOR website will, for this reason, be kept live for at least one year from the formal end of the project i.e. until June 2019.

WP11 – Economic Analysis of SENATOR’s Clinical Efficacy

The main objective of Work package 11 (WP11) was to carry out the economic analysis of the SENATOR Trial. The preliminary analysis was a literature review undertaken in order to better understand the evidence surrounding the impact of adverse drug reactions on hospital admissions in general and hospitalizations of older people in particular. The evidence suggested that 3-5% of hospital admissions may be due to a drug event. Additionally, the review confirmed that adverse drug events are responsible for highly significant costs to health systems.

The main outcomes of interest for this work package were (i) the potential reduction in avoidable adverse drugs events, (ii) the associated costs and cost savings and (iii) the impact on quality of life of patients.

In order to understand the economic analysis of SENATOR’s clinical efficacy, economic report forms were designed before implementation within the randomized controlled trial (RCT). Cost forms and resource use forms were initially disseminated across participating clinical sites and pilot tested to understand ease of use. The economic component of the electronic Case Report Form (e-CRF) was designed to collect macro- and micro-costing. Therefore, resource uses such as length of hospital stay and diagnostic procedures were included. The costs of a bed stay, emergency/A&E and outpatient appointments, and costs of diagnostic procedures were also completed by each study site.

The quality adjusted life year (QALY) was the main outcome measure within the economic analysis. The official EQ-5D forms in appropriate languages were obtained from the official EuroQol group. These translations are verified by EuroQol and are often included within studies in other European countries. The EQ-5D forms were pilot tested in Ancona, Milan and Reykjavik, and feedback was considered carefully to ensure necessary dissemination within the other sites. Further training was provided to support the implementation and collection of the EQ-5D by video-conferencing and at meetings with primary researchers.

The economic analysis of SENATOR’s clinical efficacy sought to understand the potential cost-effectiveness of the SENATOR software intervention in terms of the costs and outcomes collected. As no difference in the primary end-points of the study were found and no cost of the intervention was available (as the algorithm was still under commercial development), a cost-minimization analysis was undertaken. We also used a cost-consequence analysis (CCA) of the cost savings and QALYs in both arms as a means of assessing the potential benefits of SENATOR. Also by using the QALYs gained we were able to construct a potential cost-utility ratio that would ascertain the cost-effectiveness of the SENATOR engine under different pricing assumptions.

The costs and outcomes between the SENATOR and control arm were drawn from appropriate sources on the eCRF and analyzed. The baseline analysis was undertaken on complete cases only (n=1294) and statistical analysis performed in STATA 11®. Baseline descriptive statistics, t-tests, chi-squared and ANOVA tests were undertaken where appropriate. Cost data were adjusted using the purchasing power parity conversion (set by

OECD) and presented as an average overall and by each site in euros (€). Costs and outcomes were not discounted as the follow up period was less than one year.

The total cost per patient included hospital and non-pharmacological costs. Hospital costs in the SENATOR arm were €14,435 and €15,219 in the control arm, whilst non-pharmacological costs were €23.08 and €28.87, respectively. Amongst hospital costs, it was found that index inpatient stay, further inpatient stays, and medication costs were the main drivers for lower overall costs. The average inpatient stay for patients in the SENATOR arm was 8 bed stays, compared with an average of 10 in-patient stays in the control arm. The incremental total cost difference per patient was €790.54, favouring the SENATOR arm, however this difference was not statistically significant between the two groups. Between the arms in the different sites, SENATOR was associated with lower costs in all sites apart from Reykjavik where costs were greater in the SENATOR arm cohort. This is likely related to the number of medications and medication costs which increased over the follow-up period.

The total QALYs were estimated using the area-under-the-curve method. The utility values at baseline, 14 day follow-up/discharge and 12-week follow up were estimated using time trade-off tariffs derived from a large independent European reference value set. The average total QALY per patient for the SENATOR intervention was 0.156 and 0.156 in the control arm. The difference between the two arms in quality of life was minimal, but slightly favoured the SENATOR intervention.

In light of the SENATOR algorithm having no explicit price and uncertainty in the cost of its deployment, a sensitivity analysis surrounding the estimated cost and utility data was modelled. A threshold analysis to understand the price-point for which the SENATOR tool would be cost-effective at various values was performed. The results found that at a cost above €800 per patient, SENATOR would not be cost-effective. When an estimated cost of SENATOR deployment per patient in terms of clinician time was included, the threshold analysis result changed minimally.

Overall, the completeness of both EQ-5D and cost data was very satisfactory. Between the clinical sites, patients in Aberdeen, Madrid and Reykjavik had lower total QALYs. These patients also appeared to have slightly higher number of medications and lower inpatient bed stays compared to Cork and Ghent. However, as the differences were not statistically significant, correlations to explain the variances were not explored further. Furthermore, the purpose of the economic analysis was to understand the differences between the overall treatment and control arms and in this context, it was successful.

The economic analysis therefore presents the SENATOR intervention as having the potential to have a favourable impact on resource use/economic costs whilst maintaining patient health outcomes. The results are drawn from the results of the RCT which saw an unfortunately low level of uptake of the SENATOR recommendations among the clinicians advised to use it in the intervention arm of the trial. However, the economic impact suggests possible reductions in hospital costs and that if a medication review system such as SENATOR is well-priced, possible cost-savings and cost-effectiveness compared with standard care can be achieved, whilst maintaining the same patient quality of life.

1.4 The potential impact

Socio-economic impact and the wider societal implications of the project

The focus of the SENATOR project was the prevention of adverse drug reactions (ADRs) in older people with multi-morbid illness and associated multiple medications or 'polypharmacy'. ADRs are particularly common among older people hospitalized with acute illnesses of all kinds and result in excess morbidity and mortality. ADRs were noted to be highly prevalent at the point of arrival to hospital i.e. approximately 26% affected; in these patients, ADRs were causal or contributory to acute hospitalization. Previous single centre trials had shown that STOPP/START criteria, designed to help clinicians to avoid potentially adverse medications (STOPP) and potentially adverse prescribing omissions (START), could reduce inappropriate prescribing, ADRs, medication costs and medication-related falls in multi-morbid older people with polypharmacy. The thrust of the SENATOR project was therefore to determine if software deployment of STOPP/START criteria as well as other warnings about potentially harmful drug-drug and drug-disease interactions in the hospital environment could minimize ADRs among older multi-morbid patients. Most multi-morbid older people receive their prescriptions from prescribers who are not specialized in geriatric medicine or clinical pharmacology. Therefore, the focus of the SENATOR clinical trial was to examine if SENATOR software advice reports designed to minimize adverse pharmacotherapy offered to

clinicians other than geriatricians and clinical pharmacologists could result in a significant reduction in ADR incidence as well as lower overall healthcare costs. The SENATOR trial further sought to test the intervention's impact on patients' quality of life and levels of healthcare utilization.

Contribution to Community and social objectives

The SENATOR project has demonstrated a number of important observations. Firstly, when incident ADRs are examined using a **novel ADR detection/ascertainment system**, ADR incidence is found to be much higher than has been previously reported in the literature i.e. almost 1 in 4 patients (24.7%) who are hospitalized in major European medical centres experience ≥ 1 non-trivial ADRs during the index hospitalization. This finding is consistent with the ADR incidence observed in previous studies carried out in Cork, southern Ireland where the SENATOR project was co-ordinated. Such a high incidence of ADRs in a rapidly growing population of multi-morbid people over 80 years in particular represents a major challenge to the **patient safety agenda throughout Europe**. Given that older people who experience ADRs in hospital have prolonged hospitalizations and have higher mortality rates, there is a clear adverse economic implication arising from such a high rate of ADRs. Any intervention that minimizes ADRs in this high risk population will likely have significant positive implications for health care budgets throughout Europe.

The SENATOR project, although conceptually complex and challenging from a practical perspective, has nevertheless demonstrated that **functional software specially designed to lessen the burden of ADRs in older people with multi-morbidity and associated polypharmacy can be produced and deployed**. One of the major challenges highlighted by the SENATOR trial is that most pharmacotherapy advice points, although correct, are not implemented by attending clinicians who are not specialized in geriatric medicine or clinical pharmacology. This finding indicates that alongside novel software solutions to minimize ADRs and other elements of adverse pharmacotherapy in the growing population of older people in Europe, there **needs to be a mechanism that maximizes the uptake/adherence of pharmacotherapy optimization advice**. Greater numbers of physicians and pharmacists specialized in geriatric medicine and pharmacotherapy will very likely be required throughout Europe to direct implementation of software-delivered pharmacotherapy advice if medication-related morbidity and its consequences are to be minimized.

Main dissemination activities and exploitation of results

(A) Dissemination activities

As with most biomedical research projects, the outputs of SENATOR are being disseminated through the conventional channels of international scientific conferences and peer-reviewed journals that are referenced in the major journal databases e.g. PubMed, Science Direct, Embase. SENATOR project data have been presented at European Geriatric Medicine (EUGMS) and European Society of Clinical Pharmacy (ESCP) conferences as well as national scientific conferences in Ireland, Spain, Belgium, Iceland and Italy. So far (to August 2018), a total of 41 scientific papers arising from SENATOR work have been published in peer reviewed journals, of which 16 papers are available by open access.

A major dissemination/communication event for SENATOR took place on 21st September 2017 in Nice, the project being awarded a full symposium that was part of the main Programme of the EUGMS congress <http://www.eugms.org/2017/scientific-programme.html>. The SENATOR symposium has had an impressive audience at the 13th European Geriatric Medicine Society Congress, which is an annual event that has become one of the most important international scientific meetings in the field of Geriatric Medicine, with more than 1,500 attendees from Europe and from all over the world. The participants were given the opportunity to find out more about the project genesis and the key ideas and developments in it, but also about challenges and future plans. The Symposium was structured as follows:

Chairs: Alfonso Cruz-Jentoft (Spain), Adalsteinn Gudmundsson (Iceland);

Talks:

- Adverse drug reactions in older people and their prevention: the need for a new approach Mirko Petrovic (Belgium)
- The SENATOR Project: Genesis & Development Denis O'Mahony (Ireland)
- The SENATOR Clinical Trial: A Randomized controlled trial to evaluate the effect of SENATOR (Software ENgine for the Assessment and optimisation of drug and nondrug Therapy in Older peRsons) on the incidence of adverse drug reactions in older hospitalized patients Paul Gallagher (Ireland)

- ONTOP: Can Non-Pharmacological Interventions be recommended to prevent or reduce critical outcomes in older subjects? Antonio Cherubini (Italy)

A number of dissemination activities have also been undertaken to publicize the SENATOR project, including on-line YouTube video interviews with senior SENATOR project staff, https://www.youtube.com/watch?v=2BirU_pHp7w, <https://www.youtube.com/watch?v=iZDIEmpY3T8>, <https://www.youtube.com/watch?v=IHuoENWutyg>, https://www.youtube.com/watch?v=tm_8YHiyUtg, <https://www.youtube.com/watch?v=fAP3E7jibkE>, a specifically designed animation describing SENATOR and its objectives <https://www.youtube.com/watch?v=7fpNPWFp0is>, and national television and lay press interviews with co-principal investigators <https://www.senator-project.eu/press-area/>.

As part of the SENATOR dissemination/communication remit, a publicly accessible website was set up early in the history of the project. The website is located at: <https://www.senator-project.eu/> and contains details of the project, its work packages, its personnel and the general progress of the project as well as links to a series of on-line related videos that quickly explain the essence of the project as well as interviews with a number of the project's work package leaders. The website has been managed by ARTTIC until the end of the project; thereafter, it will be managed by UCC as the project co-ordinating institution.

(B) Exploitation of results

(i) Software to minimize ADRs

SENATOR has shown that it is feasible to design and implement software that is capable of identifying potentially adverse pharmacotherapy in multi-morbid patients exposed to polypharmacy. The target patient population in SENATOR was elderly but could have been any multi-morbid population across the age spectrum. Validated prescribing criteria and other accepted rules can be deployed in a fast, efficient and accurate way resulting in a bespoke medication advice report specific to particular patients based on their own particular multi-morbidity and polypharmacy profile. Until SENATOR, no such software existed with this particular set of sophisticated functionalities. This has significant implications for the healthcare software industry particularly those software companies seeking to develop and market software to optimize the pharmacotherapy of the growing multi-morbid older population of Europe and beyond.

(ii) ONTOP (Optimal evidence-based Non-drug Therapies for Older People)

The compendium of ONTOP evidence-based recommendations for non-drug therapies in the 15 common age-related conditions has considerable intrinsic value. ONTOP represents the first collection of its kind in the realm of non-drug treatments and provides important guidelines for physicians and therapists who routinely deal with multi-morbid older people.

(iii) SENATOR Trial Data

Although SENATOR is a 'negative' trial i.e. primary and secondary endpoints not statistically different in the intervention cohort compared to the control cohort, there are two highly important results coming from the trial that are highly important to clinical practice throughout Europe and beyond. Firstly, using the novel validated ADR detection system based on the Trigger List (*vide infra*), the incidence of non-trivial probable or certain ADRs is substantially higher among acutely ill older multi-morbid patients in hospital than was previously thought i.e. 24.7%. Secondly, having an efficient software-based system for applying inappropriate prescribing criteria and other rules to highlight potentially adverse medication and prescribing omissions is an important technological achievement. However, as the SENATOR trial shows, presenting customized reports based on these criteria/rules to patients' attending clinicians is not sufficient in itself for favourably adjusting patients' medication so that adverse pharmacotherapy is actually minimized. The fact that low level adherence among attending clinicians was observed in all 6 participating medical centres indicates that additional measures are necessary to ensure a higher level of clinician adherence with software-generated pharmacotherapy advice reports. Very likely, more specially trained physicians and pharmacists are needed throughout the European hospital network to optimize implementation of these advice reports and to provide specialist oversight of the drug therapy of older people with multi-morbidity and associated polypharmacy.

(iv) ADRROP data

The data emerging from WP01 on the design and ADR predictive capacity of the ADRROP (ADR Risk in Older Persons) scale are also important in terms of the medical science behind ADR risk calculation in older multi-morbid people. At the start of the SENATOR project, it was believed that ADR risk could be accurately calculated in multi-morbid older people; this belief was largely based on the GerontoNet ADR risk scale which was published in 2010 (Onder G et al., Arch Intern Med 2010; 170(13):1142-1148). The GerontoNet ADR risk scale had good prediction

of ADRs in older multi-morbid patients in the hospital setting i.e. AUROC values ≥ 0.70 . A subsequent study published in 2012 (O'Connor M et al. *Age Ageing*. 2012 Nov;41(6):771-6.) showed that the GerontoNet ADR risk scale had modest ADR prediction, with an AUROC value of 0.62. Using a large database from 4 studies and involving 2217 older multi-morbid patients in whom ADR occurrence was well characterized, ADRROP version 1 was constructed, tested and shown to have poor ADR prediction (O'Mahony D et al., *Eur Geriatr Med* 2018; 9(2):191-199) i.e. AUROC value of 0.62. ADRROP version 2 was constructed from high quality prospective ADR ascertainment data from the SENATOR clinical trial. Once again, ADR prediction with ADRROP version 2 was modest with an AUROC value of 0.62 once again. For these reasons, the ADRROP data show that a different approach to ADR prediction is required which is currently the basis of new research in UCC.

(v) ADR detection

The novel ADR detection/ascertainment system used in the SENATOR trial highlights how much more common ADRs are in multi-morbid older people than was previously thought. The ADR system has been internally validated as part of a PhD project conducted during the SENATOR project. The majority of ADRs experienced by multi-morbid older people in the SENATOR trial were captured by the Trigger List and subsequently confirmed by blinded experts in the majority. This finding indicates that the ADR Trigger List system offers hospitals throughout Europe and beyond a method for ADR identification that has capacity to identify the majority of ADRs in this high risk population of patients. The patient safety agenda throughout Europe should therefore benefit from widespread application of the Trigger List method of ADR detection.

Outlook and future research

- WP01 described two related data analyses aimed at producing an ADR prediction scale appropriate for use in older multi-morbid patients with polypharmacy. Construction of ADR risk scales based on several ADR risk factors is possible but the ADR risk prediction from such a model is modest at best, such that these scales cannot be recommended for routine clinical practice. Clearly, researchers must take a different approach to ADR prediction in multi-morbid older people. Alternative approaches to ADR risk assessment in multi-morbid older people must very likely take specific drugs/drug classes into consideration when calculating ADR risk. The combination of patient risk factors as well as particular drug risk factors will likely prove more effective in ADR prediction in older people.
- WP02 dealt with defining the evidence base for non-drug therapies which are commonly used alongside drug therapies in the management of older people with multi-morbid illness. The method described in WP02 should stimulate similar research aimed at defining evidence-based non-drug therapies in many other conditions that older people commonly experience. Furthermore, the task of further updating the non-drug therapy recommendations defined for the 15 ONTOP conditions will likely be taken up by researchers in the area of non-drug therapies for older people.
- WP03 described the construction of a comprehensive Drug File suitable for interfacing with SENATOR software in 6 different countries in Europe. Comprehensive Drug Files of this kind are not widely available commercially but nevertheless are highly important for international comparative research. The creation and updating of a Drug File that is appropriate to the pharmacopeia of all European countries has value and presents an opportunity to various agencies including the commercial software sector and academia.
- WP04 involved the design and construction of the SENATOR software engine which was validated in WP05 and shown to match the performance of two physicians with expertise in geriatric medicine and pharmacotherapy in the deployment of STOPP/START criteria as well as potentially serious drug-drug and drug-disease interactions. The task of interfacing STOPP/START criteria as well as drug-drug and drug-disease interaction databases with the ATC code-based Drug File was successfully completed within WP05. The commercial potential for SENATOR software is clear from WP04. Also, the deployment of SENATOR software in clinical settings other than the acute hospital environment offers research opportunities in the future.
- WP06 shows how SENATOR was successfully translated from English into 4 other languages and demonstrates how SENATOR can be adapted for use in non-English speaking countries. This has commercial implications for SENATOR and indicates how SENATOR and other similar software engines can be used by researchers outside English speaking countries.

- WP07 and WP08 show how a trial of substantial complexity can be organized and run in several countries including non-English speaking countries. Future research must clearly focus on ways of improving adherence software-generated pharmacotherapy advice reports among clinicians, particularly clinicians who encounter multi-morbid older people with polypharmacy on a routine basis. The challenge with improving adherence is likely more organizational than technical (i.e. relating to software design).
- WP09 showed that SENATOR as an intervention was safe and did not present any serious patient safety issues. This finding should give confidence to researchers and software engineers that software interventions like SENATOR should be safe for application in older people with multi-morbidity.
- WP10 Showed that interfacing electronic patient records with pharmacotherapy optimization software like SENATOR is feasible. This finding should stimulate further work in the area of clinical record design to make it possible to drive the pharmacotherapy optimization agenda alongside routine clinical work in places where there are fully electronic patient clinical records.
- WP11 examined the economic and quality-of-life dimensions to SENATOR software intervention. The high cost of ADRs in older people, both economic and personal, should provide a major stimulus to other researchers to examine ways of reducing these economic and quality of life burdens in the growing population of older multi-morbid people in Europe and throughout the world. WP11 provides practical and easily reproducible methodologies that can be adapted in future research projects of a similar nature to SENATOR.