**Abstract (250 words)**

**Background**: Multi-morbidity and polypharmacy increase the risk of non-trivial adverse drug reactions (ADRs) in older people during hospitalization. Despite this, there are no established interventions for hospital-acquired ADR prevention.

**Methods**: We undertook a pragmatic, multinational, parallel arm prospective randomized open-label, blinded endpoint (PROBE) controlled trial enrolling patients at 6 European medical centers. We randomized 1537 older medical and surgical patients with multi-morbidity and polypharmacy on admission in a 1:1 ratio to SENATOR software-guided medication optimization plus standard care (intervention, n= 772, mean number of daily medications = 9.34) or standard care alone (control, n = 765, mean number of daily medications = 9.23) using block randomization stratified by site and admission type. Attending clinicians in the intervention arm received SENATOR-generated advice at a single time point with recommendations they could choose to adopt or not. The primary endpoint was occurrence of probable or certain ADRs within 14 days of randomization. Secondary endpoints were primary endpoint derivatives; tertiary endpoints included all-cause mortality, re-hospitalization, composite healthcare utilization and health-related quality of life.

**Results**: For the primary endpoint, there was no difference between the intervention and control groups [24.5% versus 24.8%; OR 0.98 (95% CI 0.77 to 1.24; p = 0.88]. Similarly, with secondary and tertiary endpoints, there were no significant differences. Among attending clinicians in the intervention group, implementation of SENATOR software-generated medication advice points was poor (approximately 15%).

**Conclusions**: In this trial, uptake of software-generated medication advice to minimize ADRs was poor and did not reduce ADR incidence during index hospitalization.

**Key words**:

- Adverse drug reactions
- Older people
- Multi-morbidity
- Polypharmacy
- Prevention
- STOPP/START criteria
- Software

**Key points**:

- Previous single centre randomized clinical trials (RCTs) have shown that application and implementation of STOPP/START rules for avoidance of potentially inappropriate prescribing errors significantly reduced adverse drug reaction (ADR) incidence in hospitalized older people.
- SENATOR is the first large scale, multi-centre RCT assessing the effect of a software engine for electronic deployment of STOPP/START prescribing rules on incident ADRs in older people living with multimorbidity hospitalized with acute illness under the care of specialists other than geriatricians.
- Compared with patients allocated to the control arm i.e. usual pharmaceutical care, incident ADRs in patients assigned to the SENATOR software intervention arm of the SENATOR trial were comparably frequent i.e. 24.5% versus 24.8%.
- Although SENATOR software successfully and accurately deployed STOPP/START criteria alongside major drug-drug and drug-disease alerts, implementation of SENATOR prescribing advice points by attending physician prescribers is poor i.e. approximately 15%.
- For electronic prescribing advice to be effective for prevention of ADRs in hospitalized multi-morbid older patients, a further element is required over and above provision of prescribing advice reports, most likely face-to-face interaction with expert physicians or pharmacists.

## Introduction

Research consistently shows that adverse drug reactions (ADRs) in older people relate directly to polypharmacy[1] which is causally linked to multi-morbidity[2]. ADRs cause substantial morbidity and mortality among older patients in hospital[3]. In a recent US study of emergency department (ED) visits, the highest rates of ADR-related ED attendance and subsequent hospitalization across all age groups occurred in older people[4]. In relation to patient safety, ADRs in older people *during* hospitalization is particularly concerning. A systematic review by Alhawassi et al.[5] concluded that at least 10% of older patients experience ADRs that lead to hospitalization or occur during acute hospitalization itself. Female sex, multi-morbidity and polypharmacy were the main risk factors for ADRs in this population. ADRs have serious adverse effects on the health, functional status and quality of life of older people[6,7] and increase healthcare costs[8,9]. In its third Global Patient Safety Challenge in 2017, the World Health Organization in recognizing the threat from ADRs to patient safety committed to finding ways to reduce serious avoidable harm related to medications by 50% over 5 years[10].

Experts generally agree that inappropriate prescribing in older people predisposes to ADRs[11-14]. Therefore, one strategy for preventing ADRs is to screen older patients' medications using criteria for potentially inappropriate prescribing (PIP) such as Beers criteria[15] or STOPP criteria[16]. To date, there are four published single-center prospective randomized controlled trials in which application of STOPP criteria as an intervention has been compared with standard pharmaceutical care[17-20]. These trials show that routinely applying STOPP criteria significantly reduces PIP, ADR incidence, falls and medication costs in hospitalized older multi-morbid patients. However, each of these studies was single-center, not double-blinded and STOPP criteria were not automated.

Most prescribing for older people living with multimorbidity with polypharmacy is done by physicians who are not specialized in geriatric medicine or clinical pharmacology. Since age-related multi-morbidity causes polypharmacy and polypharmacy heightens PIP and ADR risk[21], routine screening for PIP among older people attended by non-specialist physicians is one logical approach to reducing ADRs. Furthermore, most deprescribing in hospital is reactive, not proactive, indicating that prescribing prompts to attending physicians may be required[22].

In recent years, systematic reviews have examined the medication optimizing impact of clinical decision support systems (CDSS) in older people living with multimorbidity in various clinical settings[23-26]. Although conclusions vary, CDSS have in general been found to reduce PIP[27]. No clinical trial, however, has examined whether CDSS-deployed PIP criteria in the acute hospital setting reduce ADRs in acutely ill multi-morbid older patients.

Therefore, the central aim of this multi-centre trial was to determine whether providing CDSS-generated medication advice reports based predominantly on PIP criteria to clinicians attending hospitalized acutely ill older people living with multimorbidity significantly reduces ADR incidence.

## Patients & Methods

We designed a pragmatic prospective randomized open-label blinded endpoint (PROBE) controlled trial involving six European medical centres (Ireland, Scotland, Spain, Italy, Belgium, Iceland). We screened patients hospitalized with acute unselected medical and surgical illness for trial enrolment. All six centres were large academic teaching hospitals which routinely received unselected acute medical cases for admission across a range of clinical specialties. Each centre has a long-established geriatric medicine service providing specialist care and advice on management of patients aged ≥ 65 years admitted under the care of specialist departments *other than* geriatric medicine. The focus of the SENATOR trial is the need to optimize the appropriateness of older patients' prescriptions to avoid ADRs. The central hypothesis in the SENATOR trial is that attending medical staff prescribers working in specialist departments other than geriatric medicine will, when offered advice points relating to potentially inappropriate medication in individual patients under their care, adjust the prescriptions of these patients according to SENATOR software-

generated advice reports (the intervention). These adjustments will, in turn, significantly reduce ADR incidence in intervention arm patients compared to matched patients receiving standard pharmaceutical care in the same medical centre. Further details are provided in a previous trial protocol paper[34] and are summarized in the **Supplementary Appendix**.

## Results

**Figure 1** shows the CONSORT flow diagram for the trial. From July 2016 through February 2018, we screened 17,657 patients and randomized 1,537 patients to intervention (n=772) or control (n=765) groups [see screening failure details in **Supplementary Appendix**]. Patient recruitment was distributed as follows: Cork 405 patients (26.4%), Reykjavik 295 patients (19.2%), Aberdeen 285 patients (18.5%), Ghent 205 patients (13.3%), Madrid 190 patients (12.4%), and Ancona 157 patients (10.2%). The median [IQR] length of stay in the control patients was 6 [3-12] days, in the intervention patients it was 6 [3-10] days. Baseline control and intervention groups were well matched at baseline [**Table 2**], with no significant differences noted for age, sex, number of daily prescription drugs, CIRS-G score, MMSE score, BI score or level of dependency (requirement for daily personal and domestic help). We randomized patients from 21 specialties i.e. 13 medical and 8 surgical clusters (see **Supplementary Appendix**), with similar proportions of patients from medical and surgical clusters in the control and intervention populations.

Eight hundred and twenty-eight trigger list adverse events occurred in the 1537 randomized patients; by Hartwig & Siegel criteria, 215 (26.0%) events were mild, 564 (68.1%) moderate, 41 (4.9%) severe and 8 (1%) fatal. There were 475 confirmed primary endpoints in 379 patients i.e. 24.7%; 84 ADRs were mild (17.7%), 364 moderate (76.6%), 24 severe (5.1%) and 3 fatal (0.6%). The primary endpoint occurred in 190 control patients (24.8%) compared to 189 intervention patients (24.5%; OR 0.98; 95% CI 0.77 to 1.24; p = 0.88). Results were similar for all secondary endpoints [**Table 3**], and post-hoc adjustment for additional covariates did not significantly affect the results.

Adherence among attending clinicians with SENATOR software-generated medication recommendations was substantially lower than expected i.e. 15.0% on average across the 6 participating sites [**Figure 2**]. The pattern of adherence with STOPP recommendations that constituted the majority of SENATOR report recommendations was also lower than expected across the six clinical sites [average 19.7%, see **Supplementary Appendix**].

As with the primary and secondary ADR-related endpoints, no significant differences were detected between control and intervention groups for any tertiary endpoints [**Table 3 & Supplementary Appendix**].

## Discussion

SENATOR is the first large scale multinational clinical trial examining the impact of a customized CDSS medication optimization intervention on incident ADRs in acutely ill older people in hospital. The trial has yielded negative results probably because intervention arm clinicians did not implement SENATOR software-generated medication recommendations at a sufficiently high frequency.

SENATOR was a pragmatic trial to test the impact of the CDSS-generated reports delivered to attending physicians on incident ADRs without other influences within the intervention. We designed the SENATOR trial protocol such that attending clinicians retained full control of their patients' drug prescriptions i.e. they could accept or reject SENATOR recommendations using their own clinical judgment in each case. The trial design followed the hypothesis that attending clinicians when presented with CDSS-generated evidence-based prescribing advice will in general apply that advice when it is deemed appropriate in individual cases. A previous single-centre trial had shown high-level adherence with STOPP/START recommendations generated without CDSS support[20]. In that trial, a trained physician provided STOPP/START recommendations at a time when a sufficiently efficient and reliable software vehicle for application of STOPP/START criteria was not available. The trained physician applied STOPP/START criteria to the medications of intervention arm patients

within 48 hours of admission and provided the details of the contravened STOPP/START criteria in person to the attending senior residents or consultants, supplemented by an individualized printed report. Although delivery of STOPP/START criteria advice by a trained physician is highly effective for ADR prevention, it is however unlikely to be cost-effective[35]. The SENATOR trial aimed to match the performance of the earlier single centre trial but in a multi-centre context using software-generated advice reports only (as distinct from physician-delivered and moderated reports) i.e. an intervention that would likely be cost-effective.

There are several possible reasons for poor prescribing advice adherence among attending clinicians observed at all six sites in the SENATOR trial. A follow-up qualitative study towards the end of trial patient recruitment using the Theoretical Domains Framework methodology[36] applied to transcribed audio-recorded interviews with 10 primary researchers and 14 physician prescribers from the six sites identified four predominant factors that influence SENATOR software advice adherence[37]. These included: (i) the computerized advice report frequently producing recommendations of low clinical relevance in the context of serious acute illness, contributing to prescriber 'alert fatigue'; (ii) the frequently busy pressurized acute hospital environment having a negative impact on timing and location of medication advice delivery; (iii) prescribers' variable level of experience/responsibility and attitude to clinical trials; (iv) patient-specific issues including clinicians' knowledge of patients' diagnostic details, medication preferences and clinical status in hospital. Other possible reasons for poor SENATOR CDSS advice implementation include belief that long-term prescribing adjustment is essentially the responsibility of patients' primary care physicians, reluctance to adjust medications outside of one's own expertise and lack of awareness about highly prevalent ADRs and the high risk of incident ADRs in multi-morbid older patients. Some SENATOR advice points may have been technically correct but not appropriate for application in certain patients during their acute illness. For example, STOPP criterion K1 which recommends avoidance of benzodiazepines in those at risk of falls may not be easy or appropriate to implement in some older patients in the context of acute illness in the hospital setting because of heightened risk of benzodiazepine withdrawal syndrome and exacerbation of clinical status.

Another theoretical reason for poor SENATOR advice implementation is very short hospital length of stay (LOS). All patients were randomized to control or intervention groups within 60 hours (the great majority within 24 hours) of admission and primary and secondary endpoints were assessed at discharge or day 14 whichever came first and the median LOS in both control and intervention groups was 6 days. Thus, whilst relatively short admissions could explain lack of implementation of SENATOR advice points in some cases, it is unlikely that this was the main reason in most intervention patients.

Because SENATOR advice implementation was poor in all centres, we contend that for future medication optimization interventions in older multi-morbid patients to succeed, ensuring medication optimization advice implementation among attending clinicians will be crucial. In previous studies, face-to-face verbal interaction with attending clinicians by trained physicians or pharmacists helped to enhance medication advice adherence[20,32] and should therefore become an integral feature of any future CDSS intervention trial design involving older patients with chronic multi-morbidity and polypharmacy.

Previous research shows that routine medication advice presented by appropriately trained pharmacists reduces inappropriate prescribing in multi-morbid older patients[38], although not to the same extent as physician-delivered advice. Notably, however, the high level of prescriber acceptance of pharmacist-delivered medication recommendations in these studies occurred in the context of specialized pharmacists working closely with geriatricians in an integrated specialist team using structured medication review[38]. The challenge for the future is how to reproduce the efficacy of such a system across the wide range of specialist departments within most large hospitals. Recent work by Quintens et al.[40] shows that routine medication appropriateness surveillance by a trained pharmacist in addition to electronic medication alerts based on an integrated computerized physician order entry system supported by a CDSS achieved 83% medication advice implementation. Electronic prompts to attending physicians alone achieved 56% adherence in the tertiary referral centre involved in that study where medical records and prescriptions were fully electronic. Interestingly, comparable STOPP and START criteria adherence (81.2% and 87.4% respectively) was achieved by O'Connor et al.[20] when STOPP/START medication advice was conveyed verbally by a senior resident in

geriatric medicine reinforced by a printed advice report. Such qualified prescribing advice may counteract some of the negative effects of adhering strictly to disease-specific guidelines contributing to "evidence-biased" overprescribing in older multi-morbid patients[39].

Using a novel ADR detection system, we recorded an overall hospital-acquired ADR incidence of 24.7% in SENATOR trial patients, substantially higher than previously reported in the literature i.e. 6.3%[42] to 11.5%[43]. Such a high ADR incidence mandates routine screening for PIP and intervention to attenuate PIP-related ADRs, thereby maintaining patient safety from adverse medication. Without such structured medication surveillance by trained physicians or pharmacists to promote better implementation of medication advice, ADRs will continue to compromise older patient safety.

There are some limitations to the present study. In the original trial design, we had calculated that for the trial to have 90% statistical power, 900 patients in either trial arm i.e. 1800 patients would be needed for randomization. Because of time and resource constraints, we randomized 1537 patients i.e. 85.4% of the target number. It is unlikely, however, that SENATOR advice implementation would have been substantially different even if we had randomized 1800 patients. Another limitation is the lack of cluster randomization with the theoretical advantage of minimizing trial contamination. However, from the earlier observational study[30] in which the eCRF was tested and subsequently refined, we discovered substantial heterogeneity in ADR incidence between the clinical sites and within particular specialties across the sites. In addition, the ADR prediction tools available were not robust enough to correct for between-cluster ADR variability in baseline ADR risk. Thus, we could not exclude the possibility that any observed differences in ADR incidence might result from unequal distribution of ADR risk at baseline. For these reasons, we decided on individual level randomization rather than cluster randomization, accepting that cross-arm contamination could in theory diminish the intervention effect size. The lack of a prior pilot evaluation of the intervention is another limitation. However, with major time and resource constraints, the SENATOR trial was already substantially delayed by the time it began such that the imperative was to proceed with the trial as per protocol. The delay with starting the trial was mainly due to unforeseen delay with completion and validation of the SENATOR software and achieving successful interface with the eCRF. Finally, a full assessment by an expert in implementation science would have been ideal prior to starting the trial. However, once again, constrained time and resources did not allow for this.

In a recent commentary, Shortliffe and Sepulveda[44] emphasized that future studies evaluating any CDSS must focus on how well a CDSS performs any clinical task compared to the same task being performed by experts. They also emphasized that any CDSS must be fail-safe, should not harm patients and should integrate easily with existing workflows. However, even with all these necessary attributes of a reliable and safe system, any CDSS must be acceptable to clinicians to be effective. In relation to medication optimization in multi-morbid hospitalized older patients, the SENATOR trial shows that a CDSS can be safe and efficient but still lack impact if attending clinicians do not implement the medication advice provided. Future trials should evaluate interventions that incorporate efficient software delivery of prescribing advice combined with direct face-to-face contact between attending clinicians and trained physicians or pharmacists who promote the principles of comprehensive geriatric assessment including pharmacotherapy optimization. We contend that for CDSS-based medication optimization interventions in multi-morbid older patients to succeed this combination is essential.

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**Table 1:** Pre-specified 'Trigger List' of adverse events which formed the basis of ADR identification and corroboration. All Trigger List events were notified to members of the blinded endpoint committee such that blinded adjudicators did not assess potential ADRs occurring in their own site.

| **Pre-specified event** | **Definition** |
|---|---|
| Fall/s | New onset of one or more falls. |
| New onset unsteady gait | New onset of unsteady gait that results in poor mobility and unsteady balance. |
| Acute kidney injury | An increase in serum creatinine by 0.3mg/dl (26.5 µmol/l) within 48 hours or an increase in serum creatinine by 1.5 baseline, which is known or presumed to have occurred within the prior 7 days. |
| Symptomatic orthostatic hypotension | A systolic blood pressure drop ≥20 mmHg ± diastolic blood pressure drop ≥10mmHg within 3 minutes of standing from the lying or sitting posture associated with symptoms. |
| Major serum electrolyte disturbance | Serum sodium < 130 mmol/l or > 145 mmol/l and/or<br>Serum potassium < 3.5 mmol/l or > 5.2 mmol/l and/or<br>Corrected serum calcium < 2.1 mmol/l or > 2.7 mmol/l. |
| Symptomatic bradycardia | Heart rate of < 50 beats/minute with symptoms. |
| New-onset major constipation | Subjective symptoms of hard stools and/or less than 3 bowel movements per week and/or supported by nursing records. |
| Acute bleeding | Melena or hematuria or hematemesis or hemoptysis with or without a drop in hemoglobin level >2g/dl (not due to rehydration) or associated symptoms (hypotension, tachycardia, pallor) or secondary renal failure. |
| Acute dyspepsia/nausea/vomiting | Subjective symptoms of acute 'indigestion'/'upset stomach' or acute abdominal pain or acute refusal to eat or acute heartburn/acid reflux or acute nausea/vomiting. |
| Acute diarrhea | New onset liquid stools reported by the patient or the nursing staff or new liquid stools detected by medical staff on physical examination or new liquid (non-solid) stools occurring more than 3 times in 24 hours. |
| Acute delirium | Confirmed by a reliable witness and meeting DSM-V* criteria. Supported by a 4AT† ≥ 4 and/or MMSE¥ < 23/30. |
| Symptomatic hypoglycemia | Symptoms with a blood glucose of < 63 mg/dl or 3.5 mmol/L. |
| Unspecified adverse event | Deleterious events not specified above e.g. acute liver failure, anaphylaxis. |

*DSM-V: Diagnostic & Statistical Manual of mental Disorders, 5th edition.

†4AT: The 4AT screening instrument for cognitive impairment and delirium.

¥MMSE: Mini-Mental State Examination.

**Table 2**: Details of baseline characteristics in randomized patients in the SENATOR trial.

| Variable | N | Total (n = 1537) | Control (n = 765) | Intervention (n = 772) |
|---|---|---|---|---|
| **Clinical site** | 6 | | | |
| Cork (Ireland) | | 405 (26.4%) | 201 (26.3%) | 204 (26.4%) |
| Reykjavik (Iceland) | | 295 (19.2%) | 147 (19.2%) | 148 (19.2%) |
| Aberdeen (Scotland) | | 285 (18.5%) | 141 (18.4%) | 144 (18.7%) |
| Madrid (Spain) | | 190 (12.4%) | 95 (12.4%) | 95 (12.3%) |
| Ghent (Belgium) | | 205 (13.3%) | 102 (13.3%) | 103 (13.3%) |
| Ancona (Italy) | | 157 (10.2%) | 79 (10.3%) | 78 (10.1%) |
| **Sex** | 1537 | | | |
| Female | | 725 (47.2%) | 358 (46.8%) | 367 (47.5%) |
| **Age (years, IQR)** | 1537 | 78 [72, 84] | 78 [72, 84] | 78 [72, 84] |
| **Education** | 1537 | | | |
| No schooling | | 37 (2.4%) | 16 (2.1%) | 21 (2.7%) |
| Primary school education only | | 561 (36.5%) | 283 (37%) | 278 (36%) |
| Some secondary education | | 281 (18.3%) | 146 (19.1%) | 135 (17.5%) |
| Complete secondary education | | 448 (29.1%) | 203 (26.5%) | 245 (31.7%) |
| Some third level education | | 55 (3.6%) | 25 (3.3%) | 30 (3.9%) |
| Complete third level education | | 155 (10.1%) | 92 (12%) | 63 (8.2%) |
| **Smoker** | 1537 | | | |
| Yes | | 108 (7%) | 52 (6.8%) | 56 (7.3%) |
| No | | 1429 (93%) | 713 (93.2%) | 716 (92.7%) |
| **Alcohol** | 1537 | | | |
| Yes | | 432 (28.1%) | 209 (27.3%) | 223 (28.9%) |
| No | | 1105 (71.9%) | 556 (72.7%) | 549 (71.1%) |
| **Domestic assistance required** | 1515* | 604 (39.9%) | 302 (39.9%) | 302 (39.8%) |
| **Personal care required** | 1515* | 384 (25.3%) | 191 (25.2%) | 193 (25.5%) |
| **CIRS-G score** | 1537 | 15 [11, 19] | 15 [11, 19] | 15 [11, 19] |
| **Fall(s) in the previous 12 months** | 1537 | 570 (37.1%) | 290 (37.9%) | 280 (36.3%) |
| **Previous documented ADR(s)** | 1537 | 669 (43.5%) | 327 (42.7%) | 342 (44.3%) |
| **Barthel Index (median [IQR])** | 1537 | 18 [14, 20] | 18 [14, 20] | 18 [14, 20] |
| **Mini-Mental State Examination (median [IQR])** | 1503* | 27 [23, 29] | 27 [24, 29] | 27 [23, 29] |
| **Number of daily medications (median [IQR])** | 1537 | 10 [8, 13] | 10 [8, 13] | 10 [8, 13] |

*Data available in less than 100% of patients.

**Table 3**: The distributions for each endpoint, as well as model estimated effects of the SENATOR intervention. Endpoint distributions are described by their counts and percentages in each category (primary; S1, S2; tertiary i.e. mortality, and re-hospitalization), and by their median, inter-quartile range, and total range (SPC, S1C, S2C). Model results comparing SENATOR (intervention) and control groups are from logistic regression for the primary endpoint, the S1 and S2 secondary endpoints, and mortality and re-hospitalization as tertiary endpoints; from Poisson regression for the SPC, S1C, and S2 secondary endpoints. Estimates are adjusted for clinical centre and medical versus surgical admission. EQ5D-3L tertiary endpoint results are presented in Table 3a of the Supplementary Appendix.

| Endpoint | N | Combined Control & SENATOR (n = 1537) | Control (n = 765) | SENATOR (n = 772) | Model results estimate (95% confidence interval); p-value |
|---|---|---|---|---|---|
| Primary | 1537 | 379 (24.7%) | 190 (24.8%) | 189 (24.5%) | OR = 0.98 (0.77 to 1.24); 0.88 |
| S1 | 1537 | 541 (35.2%) | 281 (36.7%) | 260 (33.7%) | OR = 0.87 (0.70 to 1.08); 0.20 |
| S2 | 1537 | 339 (22.1%) | 175 (22.9%) | 164 (21.2%) | OR = 0.91 (0.71 to 1.15); 0.42 |
| SPC | 1537 | 0 [0, 0] (0 to 4) | 0 [0, 0] (0 to 4) | 0 [0, 0] (0 to 4) | RR = 0.93 (0.78 to 1.11); 0.42 |
| S1C | 1537 | 0 [0, 1] (0 to 6) | 0 [0, 1] (0 to 5) | 0 [0, 1] (0 to 6) | RR = 0.88 (0.77 to 1.01); 0.08 |
| S2C | 1537 | 0 [0, 0] (0 to 4) | 0 [0, 0] (0 to 4) | 0 [0, 0] (0 to 3) | RR = 0.90 (0.74 to 1.09); 0.30 |
| Mortality (all-cause) within 30 days of randomization | 1449 | 105 (7.2%) | 51 (7.1%) | 54 (7.2%) | OR = 1.05 (0.70 to 1.57); 0.81 |
| Re-hospitalization (all-cause) at 12 weeks of discharge | 1332 | 474 (35.6%) | 231 (34.9%) | 243 (36.2%) | OR = 1.05 (0.84 to 1.32); 0.66 |

OR = odds ratio; RR = relative risk; DM = difference in means; CI = confidence interval. Key to secondary endpoints:

S1: ≥ 1 adjudicated possible, probable or certain, non-trivial, hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization.

S2: ≥ 1 adjudicated probable or certain, non-trivial, hospital-acquired, pre-specified ADRs occurring within 14 days of randomization during the index hospitalization.

SPC: Total number of adjudicated probable or certain, non-trivial hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization.

S1C: Total number of adjudicated possible, probable or certain, non-trivial, hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization.

S2C: Total number of adjudicated probable or certain, non-trivial, hospital-acquired, pre-specified ADRs occurring within 14 days of randomization during the index hospitaliz