Cover Page:

Official Title: OPTImization of Medication by transdisciplinary Assessment of drug Treatment in Elderly hospitalized patients: application of a definitive intervention by physicians or clinical pharmacists.
(OPTIMATE)

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Study Protocol OPTIMATE

Study/ Trial Title: OPTImization of Medication by transdisciplinary Assessment of drug Treatment in Elderly hospitalized patients: application of a definitive intervention by physicians or clinical pharmacists.

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1.0 Study Synopsis

Brief Title / Acronym	OPTIMATE
Full Study Title	OPTImization of Medication by transdisciplinary Assessment of drug Treatment in Elderly hospitalized patients: application of a definitive intervention by physicians or clinical pharmacists.
Study Sponsor	**University College Cork (**UCC)
Abstract (Brief)	**Background**: Recurrent hospitalization and unplanned emergency department (ED) attendance resulting from potentially inappropriate medication is an increasingly common phenomenon in older people with multi-morbidity and associated polypharmacy. With a growing older population with multi-morbidity/polypharmacy, there is a pressing need to address the increasing challenge of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) and associated problems that accentuate adverse drug reactions/events and avoidable excess morbidity. There is also an imperative to curb excess healthcare expenditure related to preventable medication-related problems. **Objective**: To test the clinical and economic impact of a multi-faceted medication optimization definitive intervention (DI) on avoidable rehospitalization and unscheduled ED attendance in multi-morbid patients aged ≥ 70 years hospitalized with acute illness. **Design**: A randomized controlled clinical trial is proposed in which it is anticipated to randomize 3 x 463 patients to one of 3 groups: (a) standard pharmaceutical care, or (b) trained physician-implemented DI, or (c) clinical pharmacist-implemented DI. **Setting**: Acute care environment in 3 large tertiary referral teaching hospitals with similar custom and practice relating to management of older people with acute illness.

Participants: Patients aged ≥ 70 years with multi-morbid illness i.e. ≥ 3 chronic medical conditions and associated polypharmacy i.e. ≥ 5 daily prescription medications admitted with acute unselected illness.

Intervention: The definitive multi-faceted intervention will consist of the following components: (i) modified structured history of medication (mSHiM), (ii) Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) screening for PIMs and PPOs using STOPP/START version 3, (iii) drug-drug interactions screening, using Stockley's Drug Interaction Checker (iv) face-to-face consultation with attending hospital physicians to discuss PIMs, PPOs, interactions and other issues, (v) pre-discharge medication review and adjustment, (vi) detailed medication adjustment discharge report to patients' general practitioners (GPs), (vii) follow-up contact with patients' GPs and community pharmacists at 1 week and 1 and 6 months post-discharge.

Patients in the control arm (standard pharmaceutical care) will receive a sham intervention i.e. modified Medication Adherence Rating Scale (MARS) questionnaire.

Outcome measures: Primary endpoints will include: (i) unscheduled readmission within 30 days post-discharge, (ii) unscheduled readmission within between 90 and 180 days post-discharge, and (iii) ED attendance within 30 days and between 90 and 180 days post-discharge. A primary composite endpoint of unscheduled readmission or ED attendance within 30 days and between 90 and 180 days post-discharge will also be ascertained. Secondary endpoints are: (i) quality of life measured by EQ5D-5L instrument (incorporating pain control) at 30 days and at between 90 and 180 days post-discharge, (ii) all-cause mortality at 30 days and at between 90 and 180 days post-discharge, (iii) first admission to residential care facility for long-term nursing care at 30 days and at between 90 and 180 days post-discharge. Treatment effects for each of the two active intervention arms (versus control) will be estimated and equivalence tests comparing the two active arms (for each outcome) will be undertaken to determine the effectiveness of the DI as delivered by a physician compared to a pharmacist.

An economic evaluation of the DI as delivered by a trained physician and by a trained pharmacist will also be undertaken, involving

- Quality Life Adjusted Year (QALY),
- cost per hospital readmission avoided, and
- cost per ED attendance avoided.

Time frame: 36 months from project start to final report submission.

	Participating centres: UCC/Cork University Hospital, University Hospital Waterford, University of Ghent/Ghent University Hospital, Health Research Board Clinical Research Facility, Cork (HRB CRF-C).
Study Design	Interventional Randomized Controlled trial.
Study Population	1389 older people presenting to hospital with acute illness for unscheduled admission lasting > 48 hours.
Entry Criteria	Inclusion Criteria: a. Age ≥ 70years b. 3 or more chronic conditions. c. ≥ 5 daily medications pre-admission, all medications taken for at least 4 weeks continuously. d. Can speak and understand English (in the two Irish medical centres), and Dutch or French in Ghent University Hospital (Ghent is predominantly Dutch-speaking). e. Can give written informed consent, or give witnessed verbal consent or have a suitable proxy who is able to give informed assent on the patient's behalf. f. Agrees to follow-up contact post-discharge up to 180 days post-discharge. g. Agrees to primary researcher contacting the GP and community pharmacist post-discharge. Exclusion Criteria: a. Terminal illness. b. Severe dementia and clearly unable to understand the purpose of the trial or give consent to participation. c. Severe communication disorder, making informed consent impossible. d. Likely to be discharged from hospital within 48 hours of arrival. e. Intensive Care Unit (ICU) admission.

	f. Primary psychiatric presenting illness. g. Unavailable for post-discharge follow-up for any reason. h. Non-accidental poisoning. i. Previous participation in medication optimization trials. j. Active participation in another clinical trial k. Infectious illness requiring strict isolation (including COVID-19 infection) blocking access of the primary researcher to the patient for enrolment. l. End-stage renal, liver or lung disease requiring organ replacement therapy. m. Admitted under the care of specialists in Clinical Pharmacology, Palliative Medicine, Clinical Oncology or Haematology. n. Admitted under the care of specialists in Geriatric Medicine in Ghent University Hospital. o. Trial participation refusal.
Estimated Study start and End Dates	Start date: 26/09 /2022 End date: 15/07/2024
Data collection and Statistical Analysis.	All OPTIMATE trial data will be collected electronically and entered on a bespoke trial proforma. Once verified as fully correct and complete, all individual participant trial data will be stored on a fully secure clinical trial database, the Castor electronic data capture system (Castor EDC) on the server located in the Netherlands. The Castor EDC system is compliant with ICH E6 GCP, GDPR, ISO 27001 and ISO 9001 standards and regulations. On completion of all OPTIMATE trial data collection, the database will be locked down and trial statistical analysis will commence. The data analysis will be completed no later than 30/11/2024 when a Final Project Report will be submitted to the Health Research Board, the trial funding body.

Dissemination of results	The results of this trial will be presented at national and international conferences and published in relevant journals.

2.0 Background and Significance of the question

2.1 Introduction

Research consistently shows that 5-6% of all acute hospitalizations result from adverse drug reactions (ADRs; Kongkaew et al.). This proportion approximately doubles in older people with multimorbidity and related polypharmacy (i.e. ≥ 5 daily prescription medications; Oscanoa et al.). Polypharmacy which results from multimorbidity predisposes to drug-related problems (DRPs), potentially inappropriate medications (PIMs), potential prescribing omissions (PPOs), medication non-adherence, medication errors and accidental overdose, all of which heighten risk of ADRs (O'Mahony). These medication-related problems can individually or in combination lead to hospitalization, more commonly in older people (Al Hamid et al.; Thomsen et al.). A recent systematic review indicates that approximately two-thirds of hospital readmissions relating to adverse medication in older people are preventable (El Morabet et al.). Previous studies show that older people in transition from hospital to the community experience prescribing errors and problems with medication information transfer more commonly, resulting in various DRPs that are commonly detrimental to patients (Laugaland et al.). Recurrent hospitalizations (including 1-month readmissions affecting at least 21.9%-22.3% of patients (McAuliffe et al.; Ravn-Nielsen et al.) and unplanned emergency department (ED) attendances arising from potentially inappropriate medication are common in multimorbid older people, and costly (Hyttinen et al.; Leendertse et al.), but preventable. Previous studies also show that older people exposed to PIMs and PPOs in the community experience excess hospitalization and ED attendance (Xing et al.; Moriarty et al.). Hence, any definitive intervention for minimizing rehospitalization/ED attendance in multi-morbid older people should include components for minimizing PIMs and PPOs.

A recent multi-centre randomized clinical trial (RCT) called SENATOR (O'Mahony et al., 2020) examined the effect of a software intervention for applying STOPP/START PIM and PPO criteria (version 2; O'Mahony et al., 2015) along with potentially adverse drug-drug and drug-disease interaction identification in hospitalized multi-morbid older patients on incident ADRs within 14 days of randomization. The trial which eventually randomized 1537 patients showed no difference in ADR incidence between intervention patients (24.5%) and control patients receiving standard pharmaceutical care (24.8%). Importantly, the overall implementation rate of software-generated medication recommendations by attending clinicians in their patients' medication lists was only 15% in the intervention arm. A previous single centre clinical trial had shown that delivery of STOPP/START recommendations in person by a trained physician resulted in 81.2% implementation of STOPP recommendations and 87.4% implementation of START recommendations (O'Connor et al.); the number needed to treat (NNT) to prevent one non-trivial incident ADR in that trial was eleven. A parallel study of STOPP/START recommendations (as part of a multi-faceted, software-supported medication optimizing intervention) being delivered in person by a clinical pharmacist resulted in STOPP recommendations being applied in 39.2% and START recommendations in 29.5% of cases

(O'Sullivan et al.). This disparity has raised important questions about the impact of pharmacists in optimizing hospitalized older multi-morbid patients' medications (Dalton et al.).

More recently, a Danish RCT (OPTIMIST trial) examined the effect of a multi-faceted clinical pharmacist-delivered intervention (basic and extended) based on medication review during hospitalization compared with standard pharmaceutical care (Ravn-Nielsen et al.). The trial concluded that applying the extended clinical pharmacist intervention which included a motivational interview with patients and post-discharge follow-up with the patients' GPs and community pharmacists significantly reduced all-cause readmission within 30 days (hazard ratio [HR] of 0.62, 95% CI 0.46-0.84) and within 180 days (HR 0.75, 95% CI 0.62-0.90) and the proportion of patients experiencing the primary composite endpoint of readmission or emergency department attendance within 180 days (HR 0.77, 95% CI 0.64-0.93) compared to matched patients receiving standard pharmaceutical care. The NNT to prevent the composite primary endpoint with the extended pharmacist intervention was 12. The cost-benefit ratio of the extended pharmacist intervention is, however, unknown. The OPTIMIST trial included adult patients over 18 and randomized a total of 1498 patients. Importantly, less than 50% of randomized patients were aged over 65. In the over-65 age group, the impact of the extended pharmacist intervention was statistically significant whilst its impact in the under-65s was not significant. Furthermore, the extended intervention showed a significant effect on the primary composite endpoint in patients of all ages taking > 8 daily drugs at admission but was not significant in patients taking ≤ 8 daily drugs. That is, the extended pharmacist intervention was particularly effective in patients over 65 taking > 8 daily medications.

A cost-benefit analysis of the physician-delivered STOPP/START intervention RCT of O'Connor et al. indicates that it was not cost-effective (O'Brien et al.); in contrast, the pharmacist-delivered intervention in the parallel RCT by O'Sullivan et al. was found to be cost-effective. However, this analysis focused only on in-hospital ADR prevention. The OPTIMATE study proposes to measure cost effectiveness of the DI from the wider public health services perspective, principally the possible benefits derived from avoidance of unscheduled rehospitalization and emergency department attendance. The cost effectiveness analysis will focus on these events, as they are the costliest consequences in financial terms of adverse medication in older multimorbid patients. Quality of life improvement arising from medication optimization interventions is an important theoretical but so far unproven potential benefit for multimorbid older people. This aspect of the DI in OPTIMATE will also be assessed by measurement of quality of life in all randomized patients during post-discharge follow-up period.

From the OPTIMIST trial findings, it is likely that a definitive intervention (DI) most likely to succeed in optimizing medication in hospitalized multi-morbid older people with polypharmacy will be multi-faceted and sustained both during and after the index hospitalization. Furthermore, the DI should incorporate detailed discussion of proposed medication adjustments with the patient, the attending hospital physician, the GP and the community pharmacist in order to maximize its implementation and impact. Additionally, based on well-established published evidence, the DI should be focused on medication optimization at all points of care transition in older people, especially hospital discharge when the risk of inappropriate medication exposure is highest (Cardwell; Weir et al.).

Given the positive results of the OPTIMIST trial arising from an extended pharmacist intervention designed to optimize medication and the positive results of the RCT by O'Connor et al., direct comparison of physician versus pharmacist delivery of the DI is logical. Furthermore, direct comparison between physician- and pharmacist-delivered DI is important since the particular healthcare professional training of the person performing the DI would have an important bearing on

the roll-out of the DI into routine clinical practice, if shown to have significant benefit for multi-morbid older people compared to usual pharmaceutical care. It is also logical to use easily measurable endpoints that are both clinically and economically important as well as being comparable to similar trials in multimorbid older people exposed to polypharmacy.

In summary, a recent multi-centre trial (OPTIMIST) showed important positive effects of the structured pharmacist intervention on post-discharge readmission/ED attendance among older patients with polypharmacy. The previous single-centre trials in Cork also showed the positive impact of physician-delivered and pharmacist-delivered medication advice interventions, both based on STOPP/START criteria. The larger-scale, international, multi-centre SENATOR and OPERAM trials based on computerized STOPP/START interventions did not show a positive impact on incident ADRs within 14 days (SENATOR) or drug-related hospitalizations within 12 months (OPERAM, Blum et al.) largely resulting from suboptimal adherence with medication advice among attending physician prescribers.

2.2 Aims of the study

(i) Primary aim: to determine if a medication optimization DI can significantly reduce all-cause re-hospitalization and unscheduled emergency department attendance at 30 days and between 90 and 180 days in multi-morbid older people exposed to polypharmacy. To achieve this, we will measure the following outcomes: Unscheduled readmission within 30 days and between 90 and 180 days post-discharge, ED attendance within 30 and between 90 and 180 days post-discharge, and a primary composite endpoint of unscheduled readmission or ED attendance within 30 and between 90 and 180 days post-discharge.

(ii) Secondary aims:

(a) To determine the effects of the DI on secondary endpoints, including quality of life (EQ5D-5L), all-cause mortality and referral to nursing home for long-term care.
(b) To compare endpoints achieved through standard pharmaceutical care (control) with those achieved through physician-delivered DI and pharmacist-delivered DI. This is to determine if DI delivery by a trained pharmacist is more/less/equally effective compared to DI delivery by a trained physician.

2.3 Research Question /Hypothesis

Hypothesis 1: A multi-faceted medication optimization definitive intervention (DI) based on explicit inappropriate prescribing criteria, potential prescribing omission criteria and drug-drug and drug-disease interaction surveillance applied following admission and pre-discharge from hospital in older people with multi-morbid illness and associate polypharmacy supplemented by structured follow-up with patients' GPs and community pharmacists as well with patients themselves results in significantly lower rates of unscheduled rehospitalization or emergency department attendance or both compared to standard current pharmaceutical care.

Hypothesis 2: The same multi-faceted medication optimization DI has an equal effect on rates of unscheduled rehospitalization or emergency department attendance or both when delivered by a trained pharmacist compared to a trained physician.

3.0 Trial Objectives and Purpose

3.1 Primary objective(s)

- To test by RCT the effects of the definitive prescribing optimization intervention delivered to attending hospital physician/prescribers on unscheduled rehospitalization or emergency department attendance or both compared to standard current pharmaceutical care.
- To compare by RCT the effects of the definitive prescribing optimization intervention delivered by trained physicians, with the effects of the definitive prescribing optimization intervention delivered by trained clinical pharmacists on unscheduled rehospitalization or emergency department attendance or both.
- To complete the RCT (including all patient follow-ups) within 24 months.
- To deliver an RCT results report within 6 months of completion of patient follow-up.
- To publish the RCT findings in a high impact biomedical journal within 6 months of completion of all trial data analysis.

3.2 Secondary objective(s) (if applicable)

- To examine the effectiveness of the definitive intervention on quality of life as measured by EQ5D-5L.
- To examine the effectiveness of the definitive intervention on all-cause mortality.
- To examine the effectiveness of the definitive intervention on nursing home disposition.
- To examine the cost-effectiveness of the definitive intervention as measured by Quality Life Adjusted Year (QALY), cost per hospital readmission avoided and cost per ED attendance avoided.

3.3 Safety Objectives (if applicable)

- To minimize the prevalence of medications to be avoided in multimorbid older people.

4.0 Description of methodology

4.1 Type of Study- study design

OPTIMATE is designed as a prospective, single-blinded, randomized controlled multi-centre study.

4.2 Recruitment of study participants

OPTIMATE will focus on patients admitted with acute medical or surgical illness admitted to Cork University Hospital, University Hospital Waterford and Ghent University Hospital. The OPTIMATE trial will be multi-centre, involving individual level patient randomization. The 3 participating centres are large university medical centres of comparable size, diversity of medical and surgical specialties and acute admission and discharge procedures. This is to ensure that the proposed trial can recruit appropriate patients who meet the inclusion criteria efficiently so that the trial can be completed within the proposed time frame.

4.2.1 Subjects Eligibility Criteria

Inclusion criteria:

I. Age ≥ 70 years (male or female).
II. ≥ 3 chronic medical conditions.
III. ≥ 5 daily medications pre-admission, all medications taken for at least 4 weeks continuously.
IV. Can speak and understand English (in the two Irish medical centres), and Dutch or French in Ghent University Hospital (Ghent is predominantly Dutch-speaking).
V. Can give written informed consent, or give witnessed verbal consent or have a suitable proxy who can give informed assent on the patient's behalf.
VI. Agrees to follow-up contact post-discharge up to 180 days post-discharge.
VII. Agrees to primary researcher contacting the GP and community pharmacist post-discharge.

Exclusion criteria

I. Terminal illness.
II. Severe dementia and clearly unable to understand the purpose of the trial or give consent to participation.
III. Severe communication disorder, making informed consent impossible.
IV. Likely to be discharged from hospital within 48 hours of arrival.
V. ICU admission.
VI. Primary psychiatric presenting illness.
VII. Unavailable for post-discharge follow-up for any reason.
VIII. Non-accidental poisoning.
IX. Previous participation in medication optimization trials.
X. Participation in another clinical trial.
XI. Infectious illness requiring strict isolation (including COVID-19 infection) blocking access of the primary researcher to the patient for enrolment.
XII. End-stage renal, liver or lung disease requiring organ replacement therapy.
XIII. Admitted under the care of specialists in Clinical Pharmacology, Palliative Medicine, Clinical Oncology or Haematology.
XIV. Admitted under the care of specialists in Geriatric Medicine in Ghent University Hospital.
XV. Trial participation refusal.

4.3 Sampling and Randomization (if applicable)

To test the main study hypothesis i.e. that the definitive intervention (DI) yields significantly better outcomes than standard pharmaceutical care (control), patients will be randomized in a 1:1:1 ratio to one of 3 trial arms: (a) standard pharmaceutical care as it contemporaneously exists in that hospital, or (b) trained physician-delivered intervention or (c) clinical pharmacist-delivered intervention. The 3-way randomization to control, Physician-DI and Pharmacist DI is fundamental to addressing the important secondary question: does physician-delivered DI offer any advantage over pharmacist-delivered DI?

The sample size is based on a known 180-day risk of medication-related readmission of approximately 20%. At a bilateral 5% significance threshold and 80% power, for detection of an 8% absolute reduction in readmissions, with a 1:1:1 randomization, each group must contain 324 patients i.e. 972 patients in total. With the expectation of up to 30% patient attrition, we aim to randomize 972/(1-0.3) = 1389 patients.
The randomization will be designed by the trial statistician, but the code to create the resulting randomization lists will be executed by an independent statistician. The resulting lists will be integrated into the electronic data capture system in a manner such that trial staff never have access to the lists. Allocation of enrolled patients into treatment arms will then be delivered using a web-based system, such that the allocation remains concealed until a patient is unambiguously consented and enrolled onto the trial and cannot be altered in the underlying database once it is revealed. While the intervention will be known to clinical staff, the trial statistician and outcome assessors will remain blinded until the results are finalized.

Within 72 hours of admission, patients who are potentially suitable for trial enrolment will be approached by the primary researchers (PRs) and informed about OPTIMATE in outline. If they meet inclusion criteria and do not have exclusion criteria, they will be asked to provide informed consent to trial enrolment. Recommended best practice for assessment of decision-making capacity of older patients who may be suitable for the OPTIMATE trial, involves formal assessment of capacity. Where necessary, the patient's mental capacity will be evaluated using the OPTIMATE **Decision-Making Capacity Functional Assessment** guidelines document in the OPTIMATE Manual of Operations. The patient will then be randomized to either the control arm (usual pharmaceutical care), pharmacist-delivered DI arm or physician-delivered DI arm of the trial. Randomization will proceed in a 1:1:1 ratio. The randomization process will be performed electronically using Castor EDC's block randomization algorithm. Patient enrolment will be sequential. With individual level randomization, there is the theoretical risk of control group contamination. This is where both control and intervention patients could be under the care of the same physician, thereby presenting a risk of medication advice learnings in intervention patients being applied unwittingly to control patients. However, in practice, as was seen in the pre-SENATOR observation study (Lavan et al.), variation in reported incidence of ADRs across various medical and surgical specialties in the 6 multi-national participating clinical sites was so large that meaningful cluster randomization was considered both impractical and unnecessary. Furthermore, in the SENATOR trial itself (O'Mahony et al.), although uptake of medication optimization advice was generally poor, there was no evidence of contamination of the control population.

Randomization will be stratified by study site and by admitting service type (i.e. medical vs. surgical). The stratum-specific randomization lists will be generated electronically within Castor EDC, using a validated variable block randomization model. Once a patient has given consent and been enrolled onto the study, their data will be irreversibly added to the study database. From this point, the

primary researchers will receive randomization outcomes immediately upon activating the randomization request on the electronic Case Report Form (eCRF) within the Castor EDC.

4.0 Study Procedures and Schedule of Events

The schedule of trial procedures for patient participants in the intervention arm of the trial are shown in Tables 1a and 1b below. To mimic the intervention for blinding purposes of the participants, both control and intervention arm patients will receive a sham intervention in the form of a modified version of the Medication Adherence Rating Scale (MARS; Thompson et al.).

Table 1a: Schedule of events for intervention patients

Timepoints	**0/1**	**2**	**3**	**4**	**5**
Study Visit	**Baseline** (within 72 hours of admission)	**Pre-discharge** (within 48 hours pre-discharge)	**1 Week Follow-up** (within 10 days post-discharge)	**1 Month Follow-up** (within 30 days post-discharge)	**6 Month Follow-up** (between 90 and 180 days post-discharge)
	Day 1	Day variable	Day 10 (+/-3 days post-discharge)	Day 30 (+/- 7 days post-discharge)	Between Day 90 and Day 180 post-discharge
Inclusion / Exclusion criteria	X				
Decision-Making Capacity Functional Assessment	X	X**		X**	X**
Informed consent/ proxy assent	X	X**		X**	X**
Patient Demographics	X				
Medical History	X	X		X	X
Medication Reconciliation	X	X		X	X

FORTA* criteria	X	X		X	X
Laboratory Results	X	X			
Electrocardiogram review	X				
EQ5D-5L				X	X
Randomization	X				
Medication History (modified SHiM)	X				
Modified Medication Adherence Rating Scale (mMARS)	X				
Barthel Index Score	X	X			
Drug-drug interactions (Stockley's)	X	X		X	X
STOPP/START criteria (PIMs & PPOs*)	X	X		X	X
Face-to-face discussion with senior attending physician or senior resident to highlight potentially inappropriate PIMs and PPOs	X	X			
Face-to-face discussion with patient or nominated proxy (where patient does not have decision-making capacity) to explain details of recommended medication changes.		X			

Pre-discharge medication review, documentation of agreed medication adjustments and preparation of report for patient's GP with detailed explanation of recommended medication changes.		X			
Telephone contact with patient's GP to discuss medication changes.			X		
Telephone contact with patient or nominated proxy (where patient does not have decision-making capacity) to define current list of medications, discuss any medication issues and ascertain endpoint information.				X	X
Telephone contact with patient's pharmacist to define medication currently dispensed.			X	X (if necessary)	X (if necessary)
Telephone contact with patient's GP for endpoint ascertainment (if not available from patient or proxy).				X (if necessary)	X (if necessary)
Unscheduled Readmission Determination				X	X
Unscheduled Emergency Department Attendance Determination				X	X

Admission to residential care facility (long-term)				X	X
All-cause mortality check via registries or if necessary, with the patient's GP.				X	X

Table 1b: Schedule of events for control patients

Timepoints	**1**	**2**	**3**	**4**	**5**
Study Visit	**Baseline** (within 72 hours of admission)	**Pre-discharge** (within 48 hours pre-discharge)	**1 Week Follow-up** (within 10 days post-discharge)	**1 Month Follow-up** (within 30 days post-discharge)	**6 Month Follow-up** (between 90 and 180 days post-discharge)
	Day 1	Day variable	Day 10 (+/-3 days post-discharge)	Day 30 (+/- 7 days post-discharge)	Between Day 90 and Day 180 post-discharge
Inclusion / Exclusion criteria	X				
Decision-Making Capacity Functional Assessment	X	X**		X**	X**
Informed consent/ proxy assent	X	X **		X**	X**
Patient Demographics	X				
Medical History	X	X		X	X
Medication Reconciliation	X	X		X	X
FORTA* criteria	X	X		X	X

Laboratory Results	X	X			
Electrocardiogram review	X				
EQ5D-5L				X	X
Randomization	X				
Modified Medication Adherence rating Scale (mMARS)	X				
Barthel Index	X	X			
Telephone contact with patient or next-of-kin to define current list of medications, discuss any medication issues and ascertain endpoint information.				X	X
Telephone contact with patient's pharmacist to define medication dispensed.			X	X (if necessary)	X (if necessary)
Telephone contact with patient's GP for endpoint ascertainment (if not available from patient or proxy).				X (if necessary)	X (if necessary)
Unscheduled Readmission Determination				X	X
Unscheduled Emergency Department Attendance Determination				X	X

Admission to residential care facility (long-term)				X	X
All-cause Mortality check via registries or if necessary, with the patient's GP.				X	X

* PIMs – Potentially Inappropriate Medications; PPOs – Potentially inappropriate Prescribing Omissions; FORTA Fit fOR The Aged
** If necessary i.e. applies to participants who initially lacked decision-making capacity at the time of their enrolment.

6.0 Outcome measures

6.1 Primary Outcome

(i) unscheduled readmission within 30 days post-discharge,
(ii) unscheduled readmission between 90 and 180 days post-discharge, and
(iii) ED attendance within 30 and between 90 and 180 days post-discharge.

A primary composite endpoint of unscheduled readmission or ED attendance within 30 and between 90 and 180 days post-discharge will also be ascertained.
Treatment effects for each of the two intervention arms versus the control arm will be estimated for each outcome. Equivalence tests comparing the two active arms (for each outcome) will be done to compare DI delivery by physician with DI delivery by pharmacist.

6.2 Secondary Outcome(s)

(i) quality of life measured by EQ5D-5L instrument (incorporating pain control) at 30 days and at between 90 and 180 days post-discharge,
(ii) all-cause mortality at 30 and between 90 and 180 days post-discharge,
(iii) occurrence of first admission to residential care facility for long-term nursing care at 30 and between 90 and 180 days post-discharge.

The EQ-5D-5L is a self-assessed, health related, quality of life questionnaire which brings the patient (and often their carer) to the fore when attempting to measure the impact of the intervention (see Appendix 1). The scale measures quality of life on a 5-component scale including mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. It offers the patient the opportunity to express their satisfaction (or not) with the intervention received and is used to determine and quantify the benefits of the intervention.

6.3 Tertiary endpoint(s)

Our study, in line with current recommended practice (HIQA guideline, see references), proposes to examine the DI cost-effectiveness from the wider public health services perspective including possible costs and benefits accrued via the community services and rehospitalizations. The study aims to assess

the following cost-effectiveness measures of the DI as delivered by a trained physician and by a trained pharmacist:

(i) Quality Life Adjusted Year (QALY),
(ii) cost per hospital readmission avoided, and
(iii) cost per ED attendance avoided.

For the economic analysis, all ED attendances and all unscheduled readmissions of all randomized patients will be taken into account, as well as the quality-of-life status of all followed up randomized patients (EQ5D-5L; see Appendix 1)).

6.3 Safety outcomes (if relevant)

FORTA criteria (Kuhn-Thiel et al.) will be applied at baseline, at discharge, at day 30 and at day 180. FORTA criteria are validated explicit indicators of medication appropriateness. FORTA criteria category D in particular identify those medications that should be avoided in individual cases. Other FORTA labels range from A (indispensable) to B (beneficial), to C (questionable). FORTA criteria will provide an objective measure of medication safety in OPTIMATE. Patients in the 3 arms of the trial will be compared in terms of proportions with FORTA category A, B, C and D medications as indicators appropriateness/inappropriateness of medication.

7.0 Data Management and Statistical Analysis

7.1. Data Management

The research team will engage closely with HRB data stewards based in the Statistics and Data Analysis Unit (SDAU) of the UCC HRB CRF-C. Before study initiation, study staff will be instructed by members of the SDAU on data collection, organization and eCRF entry techniques that adhere to the FAIR data principles and will guide development of the study data management plan.

The data obtained in OPTIMATE will include details of patients' age, sex, physical function, cognitive function, clinical diagnoses, medications, drug doses, laboratory test results indicating kidney and liver function, quality of life and survival at follow-up. Overall, the study will enroll approximately 1400 patients across three participating medical centres. The entire data collection is not expected to exceed 100 GB of digital storage.

Data collection will be performed using a third-party electronic data capture (EDC) system ensuring consistent data entry, documentation and security between research sites. Where applicable, variable data measurements will be recorded using international standardized units. All variables are to be recorded within Comma Separated Value (.csv) data tables. Data files will include metadata identifying title, creator, keywords etc. in line with the Dublin Core Metadata Initiative alongside accompanying data dictionaries which will be developed in parallel. Medical coding of adverse events (MedRA) and medications (WHODrug) will be enacted as part of the EDC platform. Throughout the OPTIMATE study, routine data visualization and exploration approaches using the R statistical computing and graphics language will be performed. This will allow for the development of standardized documentation of both data review and reporting processes, in collaboration with the SDAU, that is both reproducible and linked to version control strategies.

Data storage and back-up will be dictated by the EDC supplier allowing for two-factor authentication and establishment of defined user access permissions and audit trails. All OPTIMATE trial data will be collected electronically and entered on a bespoke trial proforma. Once verified as

fully correct and complete, all individual participant trial data will be stored on a fully secure clinical trial database, the Castor electronic data capture system (Castor EDC) on the server located in the Netherlands. The Castor EDC system is compliant with ICH E6 GCP, GDPR, ISO 27001 and ISO 9001 standards and regulations. Pre-existing UCC IT research infrastructure protocols will provide for secondary backups of the OPTIMATE trial data. All personally identifiable data relating to participating patients is subject to General Data Protection Regulation (GDPR) and the Irish Health Research Regulations. Accordingly, all staff with data access permissions will be required to undergo training in GDPR to ensure that all data collected for the purposes of the OPTIMATE trial will be treated with the highest standards of security and confidentiality. Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals , HSE South Eastern Area Research Ethics Committee for the University Hospital Waterford Centre and from the : Commissie voor Medische Ethiek van het UZ Gent/Committee on Medical Ethics Ghent University Hospital for Ghent University & Ghent University Hospital. This study will also follow the guidelines set out by the UCC code of Research Conduct and Research Integrity.

Participation in the OPTIMATE trial and the identity of the subjects, both those screened and those enrolled and randomized, will be treated as confidential and no participant identifiable records or results relating to the study will be disclosed to any third party other than the authorized investigators. Personal identifiers will undergo pseudonymization. An encryption key, held securely away from the data, will be accessible to the project Principle Investigator at the coordinating site only.

Consent from patients participating in OPTIMATE will be obtained for all data to be shared publicly, such as data used in the generation of publications arising from the study, and in accordance with CRF-C Standard Operating Procedures. Data sharing repositories will be formerly identified via careful alignment of the expected data object outputs and evaluated using the re3data resource (re3data.org). This is to ensure maximum utility and interoperability of the final data package(s) and assignment of a persistent digital object identifier (DOI). Additional post-study data provenance will be enacted through sharing of analysis scripts and study protocols via Open Science Framework projects with an accompanying DOI(s) and/or through the HRB Open Research publishing platform.

7.2. Statistical Analysis

Treatment effects for each of the two active intervention arms (versus control) in terms of binary outcomes (e.g. readmission) will be estimated using logistic regression, while Health Related QoL (EQ-5D 5L) will be analyzed using ordinal regression with a logit link function (i.e. a proportional odds model). We will report two models for each outcome: one adjusted for centre and admitting service type; and another further adjusted for age (years), sex, number of comorbidities at baseline, and number of prescribed medications at baseline. Effect estimates will be reported as odds-ratios with 95% confidence intervals and exact p-values. There will be no correction for multiplicity, but we will report results for all outcomes regardless of the result and provide enough information for the reader to make whatever corrections they may consider appropriate. Equivalence tests comparing the two active arms (for each outcome) will be done using a "two one-sided tests" procedure based on a 90% confidence interval (which equates to a 5% type 1 error rate). All analyses will be conducted on an intention-to-treat basis and will be conducted under the quality system and SOPs of the HRB CRF-C Statistics and Data Analysis Unit. A complete statistical analysis plan (SAP) will be pre-registered on the Open Science Framework prior to database lock. Any necessary deviations from this SAP will be documented and explained in the trial report. There will be only one single trial data analysis at the end of the project. All reporting will be carried out in accordance with CONSORT guidelines for clinical trials.

8.0. Data Protection and Confidentiality

All relevant national and local requirements regarding data protection, including GDPR and Health Research Regulations, will be adhered to. Patient data in OPTIMATE will be pseudonymized. Pseudonymity of patient data is assured by means of the unique study ID number allocated on enrolment. Throughout the study, participants will be identified by this study ID number. The master key that links clinical data to participants' identities will be stored securely in each study centre.

Participants will receive a copy of the Sponsor Data Protection Notice (DPN). The DPN will inform them of their rights about their data and provide contacts for Sponsor Data controller and Data protection commissioner.

Participants will also be informed that study monitors, representatives of the sponsor and the Ethics Committee may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with legal data protection requirements.

UCC research Data protection officer will review the protocol and study documents as required by UCC policies and procedures.

9.0 REC approvals and Governance

This trial has been reviewed by and received approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals the HSE South Eastern Area Research Ethics Committee for the University Hospital Waterford Centre and from the Commissie voor Medische Ethiek van het UZ Gent/Committee on Medical Ethics Ghent University Hospital for Ghent University & Ghent University Hospital. A consent declaration was applied for, for the patients that lack decision-making capacity, through the Health Research Consent Declaration Committee (HRCDC). The application was made and conditional approval was granted on 17th July 2022. The PI has confirmed acceptance of the conditions.

In accordance with recommended practice relating to definitive clinical trials, the following oversight committees will be established for OPTIMATE: (i)Trial Management Group and (ii) Trial Steering Committee (TSC). The TMG will include the trial co-PI's, the UCC CRF-C director, the trial statistician and the trial manager. The TMG will meet formally monthly. Formal minutes of each TMG meeting will be kept and approved at each follow-on meeting. The TMG will address all matters relating to the preparation, organization, running and completion of OPTIMATE. The TMG will monitor patient recruitment and ensure that recruitment targets are achieved in order to avoid serious delays and avoidable deviations from the trial timeline.

The TSC will consist of two senior academic physicians in Geriatric Medicine and General Practice, a senior academic pharmacist and two non-clinical older persons (as per PPI description). There will be a gender balance within the TSC. The TSC will ensure a high standard of research and monitor the progress of the trial. It is proposed that the TSC will meet every 3 months and that all meetings will be minuted for the trial log. The TSC will also advise on dissemination of trial results.

A separate Data Monitoring Committee (DMC) is not considered necessary for the OPTIMATE trial because it is fundamentally a low-risk trial i.e. all advice points provided as part of the definitive intervention are evidence-based already, comply with current established best practice and are left

to the clinical judgement of the attending physician in terms of what to adopt or reject during medication review of patients enrolled in the trial. It is proposed that the TSC will also undertake the core roles and responsibilities of a DMC i.e. to regularly assess and advise on the data emerging from the trial, relevant safety data, the critical efficacy endpoints, and whether to recommend to the trial sponsor to continue, modify or stop the trial.

The entire OPTIMATE members will have up-to-date GCP training and certification (this is provided by the UCC CRF-C). The PI/coordinator will meet weekly with the trial manager to ensure that all current issues and project targets are discussed and achieved on time. All project targets (see Gantt chart) will be monitored closely by the PI/coordinator, the trial manager and a UCC CRF-C management team member.

The TMG will meet by teleconference on a monthly basis to discuss progress. There will be a rolling agenda with formal minutes to facilitate internal trial progress scrutiny. Issues relating to patient enrolment raised by primary researchers will form part of the monthly teleconference to ensure that any recurring or systematic problems relating to OPTIMATE trial recruitment are discussed comprehensively and corrected efficiently.

10.0 Insurance

The sponsor of the study, University College Cork, has appropriate insurance in place to cover litigation that may arise as a result of patients who are harmed as a result of participation in this trial.

11.0 Potential Risks of the intervention and the study procedures: (if applicable)

11.1 Adverse Event reporting (if applicable)

Adverse clinical events are expected to occur with a substantially high frequency in the patient population participating in OPTIMATE, given their age, comorbidity and frailty profile.

The definitive intervention (DI) to be deployed in OPTIMATE is considered intrinsically low risk, given that all of the advice points to be offered to patients' attending hospital medical staff and GPs are evidence-based and may be accepted or rejected by the patients' hospital doctors or GPs as they see fit.

Nevertheless, errors may possibly occur if primary researchers use patients' data incorrectly when applying STOPP/START criteria or Stockley's drug interaction software in the detection of drug-drug and drug-disease interactions.

Any actual or suspected significant adverse events experienced by patients arising out of application of the DI will be reported by the primary researcher to the following personnel within 24 hours of detection:

(i) The trial PI.
(ii) The local trial co-PI where the adverse event has been detected.
(iii) The independent trial monitor.

The PI will co-ordinate an online discussion of the suspected adverse event within 48 hours of receiving notice of the event with the local trial PI, the primary researcher who has reported the adverse event and the independent trial monitor. If there is consensus that a clinically significant adverse clinical event arising out of applying the intervention has occurred, the adverse event will be reported to the TSC). The TSC chairperson will convene a meeting of the TSC within one week of notification to examine the details of reported potential adverse event and report back to the TMG within 24 hours of its deliberations.

Any adverse event deemed potentially attributable to incorrect/erroneous application of the DI, in the judgement of the local trial co-PI, will be investigated fully by the independent trial monitor within 2 weeks of the adverse event report.

An electronic record of all reported adverse events possibly relating to the application of the DI will be kept securely at the UCC Clinical Research Facility as part of the OPTIMATE trial record for further scrutiny/examination.

11.2 Deviations from the Protocol

Any Deviations from the protocol will be noted by the PI or researchers. Any deviations which have the potential to affect participant safety, or the integrity of the study data will be reported to the sponsor i.e. Health Research Board.

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12.0 Withdrawal of Participants from the study - (If relevant)

Patient participants in the OPTIMATE trial may withdraw from the study at any time. Their data up to the time of withdrawal will be retained for later analysis unless a participant explicitly indicates that he/she wishes to have their data removed from the trial database.

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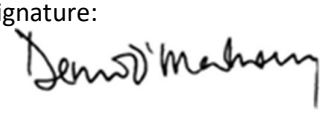
14.0 Approval and Agreement to the Protocol

The Principal Investigator agrees to perform the clinical study as written and to abide by this protocol except in case where deviation is necessary for urgent safety reasons.

Principal Investigator

Prof. Denis O'Mahony

Signature:



Date 13/06/2023

Appendix 1: Eq-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort □

ANXIETY / DEPRESSION

I am not anxious or depressed □

I am slightly anxious or depressed □

I am moderately anxious or depressed □

I am severely anxious or depressed □

I am extremely anxious or depressed □

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐