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ORIGINAL ARTICLE

Quality indicators for appropriate in-hospital pharmacotherapeutic stewardship: An international modified Delphi study

Rashudy F. Mahomedradja[1,2] | Jelle Tichelaar[1,2] | Lidwine B. Mokkink[3,4] | Kim C. E. Sigaloff[1,2] | Michiel A. van Agtmael[1,2]

[1]Department of Internal Medicine, Unit Pharmacotherapy, Amsterdam UMC location Vrije Universiteit Amsterdam, De Boelelaan 1117, Amsterdam, The Netherlands

[2]Research and Expertise Center in Pharmacotherapy Education (RECIPE), De Boelelaan 1117, Amsterdam, The Netherlands

[3]Department of Epidemiology and Data Science, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[4]Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Correspondence
Rashudy F. Mahomedradja, Department of Internal Medicine, Unit Pharmacotherapy, Amsterdam UMC location Vrije Universiteit Amsterdam, PO Box 7057, 1007 MB Amsterdam, The Netherlands.
Email: r.mahomedradja@amsterdamumc.nl

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Aims: In-hospital prescribing errors may result in patient harm, such as prolonged hospitalisation and hospital (re)admission, and may be an emotional burden for the prescribers and healthcare professionals involved. Despite efforts, in-hospital prescribing errors and related harm still occur, necessitating an innovative approach. We therefore propose a novel approach, in-hospital pharmacotherapeutic stewardship (IPS). The aim of this study was to reach consensus on a set of quality indicators (QIs) as a basis for IPS.

Methods: A three-round modified Delphi procedure was performed. Potential QIs were retrieved from two systematic searches of the literature, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. In two written questionnaires and a focus meeting (held between the written questionnaire rounds), potential QIs were appraised by an international, multidisciplinary expert panel composed of members of the European Association for Clinical Pharmacology and Therapeutics (EACPT).

Results: The expert panel rated 59 QIs and four general statements, of which 35 QIs were accepted with consensus rates ranging between 79% and 97%. These QIs describe the activities of an IPS programme, the team delivering IPS, the patients eligible for the programme and the outcome measures that should be used to evaluate the care delivered.

Conclusions: A framework of 35 QIs for an IPS programme was systematically developed. These QIs can guide hospitals in setting up a pharmacotherapeutic stewardship programme to reduce in-hospital prescribing errors and improve in-hospital medication safety.

KEYWORDS
clinical pharmacology, Delphi procedure, hospital setting, quality indicators, stewardship

The authors confirm that the Principal Investigator for this paper is Michiel van Agtmael.

1 | INTRODUCTION

Prescribing medicines is a cornerstone of in-hospital care, but it is susceptible to error. Prescribing errors (PEs) are associated with patient harm, such as quality-of-life impairing adverse drug reactions (ADRs), prolonged hospitalisation, hospital (re-)admission and even death.[1–6] Approximately 5–7% of all hospital admissions in economically developed countries are medication-related.[7,8] The European Medicines Agency (EMA) estimates that 0.3–9.1% of hospital admissions in European are medication related.[9,10] The associated global cost is US$42 billion annually.[7,10–12] In addition to the impact on patients and their families, PEs also have an emotional impact on prescribers and other healthcare professionals involved.[13,14] In-hospital PEs are a global challenge[15,16] and strategies are needed to reduce patient harm, pressure on health services and associated costs. A number of interventions have been implemented to reduce PEs. Examples include the use of Computerized Physician Order Entry (CPOE) and Clinical Decision Support Systems (CDSS),[17–21] educating medical students and residents in appropriate prescribing,[22–25] and the inclusion of specialists with expertise in appropriate prescribing, such as clinical pharmacists, in clinical wards or teams.[26–30] Although these interventions have been shown to protect against PEs in the trial context, in-hospital PEs and associated harms still occur in daily practice,[31–33] requiring a different approach to address this global challenge. In-hospital PEs are the result of a complex interplay of multiple facilitating and protective factors, multiple stakeholders and setting-specific needs and challenges.[31,32] Effective and sustainable strategies should therefore be tailored to specific in-hospital settings, focus on multidisciplinary collaboration and target the multiple factors influencing in-hospital PEs. We propose a novel approach, *in-hospital pharmacotherapeutic stewardship (IPS)*, similar to antimicrobial stewardship, which promotes the responsible use of antimicrobials through a coherent set of actions.[34] To reduce in-hospital PEs and promote appropriate in-hospital prescribing, applicable and evidence-supported quality indicators (QIs) are needed to reliably measure the quality of care achieved with this approach.[35,36] Therefore, the aim of this modified Delphi study was to develop, in collaboration and consensus with international experts affiliated to the European Association of Clinical Pharmacology and Therapeutics (EACPT), a set of QIs that could form a framework for IPS as a first step towards sustainable reduction of in-hospital PEs and associated harm.

What is already known about this subject

- Despite several interventions over recent years that have shown to be protective against prescribing errors in the trial context, in-hospital prescribing errors and associated harm still occur in daily practice.
- Intervention studies conducted thus far have focused on specific patient populations, have been mainly pharmacist-led and often solely focus on one factor influencing prescribing.
- In-hospital PEs are the result of a complex interplay of multiple facilitating and protective factors, multiple stakeholders and setting-specific needs and challenges.

What this study adds

- In collaboration and consensus with international experts affiliated to the European Association of Clinical Pharmacology and Therapeutics (EACPT), a set of quality indicators forming a framework for In-hospital Pharmacotherapeutic Stewardship (IPS) was established.
- A critical first, international step was made to introduce a novel approach, In-hospital Pharmacotherapeutic Stewardship (IPS), and to combat the complex challenge of reducing the number of in-hospital PEs and associated harm.

2 | METHODS

A three-round modified Delphi procedure was used to develop a set of evidence-based QIs for three domains of care: Structure, reflecting the healthcare setting's organisation; Process, reflecting the care delivered to eligible patients; and Outcome, reflecting the consequences and patient outcomes of interventions[35,37–41] (Figure S1). This study followed the Consolidated Criteria for Reporting Qualitative Research (COREQ), using a 32-item checklist for interviews and focus groups (Table S1). The Medical Ethics Revew Board of the Amsterdam UMC—location VUmc approved the study procedures (no. 2021.0221).

The study ran from 7 June to 1 November 2021. There were three phases: 'the preparation phase', which included preliminary research to identify ongoing or overlapping work, the extracting and drafting of potential QIs based on two literature searches and the selection of an international expert panel; 'the study phase', which included three Delphi rounds (two web-based, written questionnaires with a virtual focus between the questionnaires); and 'the completion phase', which included the finalisation of the IPS framework (Figure 1).

2.1 | Steering Committee

A four-member Steering Committee was responsible for initiating, guiding, evaluating and making final decisions in this study (Table S2). One Steering Committee member (RM) was the coordinating researcher and the only person with access to participant identification. The Steering Committee members did not participate in the study phase.

** EACPT = European Association of Clinical Pharmacology & Therapeutics*

*** R1 = first Delphi round; R2 = second Delphi round; R3 = third Delphi round.*

FIGURE 1 Schematic overview of the three phases of the study's procedures.

2.2 | Phase 1: Preparation phase

A preliminary search identified published or ongoing studies that met the study's aim. We performed a scoping search in PubMed and an advanced search in the Core Outcome Measures in Effectiveness Trials (COMET) database (www.comet-initiative.org). Full search strategies are provided in Table S3.

2.2.1 | Extraction and draft of potential quality indicators

Two comprehensive search strategies, both in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[42] were used to identify potential QIs. Both search strategies were developed in collaboration with a medical information specialist, using the electronic databases PubMed, EMBASE and the Cochrane Library. The first search was designed to identify facilitating and protective factors influencing in-hospital PEs.[31] The second search was to identify all prospective interventions reported in the literature to reduce or prevent PEs in adult in-patients (*under review*). Inclusion and exclusion criteria are described globally in Table S4 to increase transparency.

2.2.2 | Selection of the international expert panel

One hundred and eight active members of the EACPT were contacted by email to inform them of the aims and procedures of the study and to invite them to participate (initially invited experts). Clinical pharmacologists were invited because of their expertise and involvement in the safe, rational, effective and economical use of drugs. These professionals work in academia, industry, hospitals and/or government, thus providing a multidisciplinary and diverse point of view regarding in-hospital PEs.[43]

Irrespective of their participation, each member was able to suggest other professionals who they felt should be included (snowball sampling). If not included in the initial invitation, the coordinating researcher contacted the nominated experts by email.

All experts were asked to contribute their points of view based on their own experience rather than on research or (inter)national guidelines. Participation was voluntary and informed consent was obtained for each Delphi round. No financial compensation was offered for participation.

2.3 | Phase 2: Study phase

The two web-based, written questionnaires used in the first Delphi round (R1) and the third and final Delphi round (R3) were built in an electronic case report form (eCRF) by Castor EDC (www.castoredc.com). Each written questionnaire was tested for functionality, comprehensibility and comprehensiveness (face validity) before it was sent to the expert panel. The written questionnaire used in R1 was tested for face validity by all members of the Steering Committee and three other clinical pharmacologists (in training) and adjusted by the coordinating researcher (RM). The three clinical pharmacologists (in training) were subsequently invited to participate in the current study. The

written questionnaire used in R3 was tested for face validity by a member of the Steering Committee (JT) and adapted by the coordinating researcher (RM).

Each expert received a personal link via email to access the written questionnaires. They were asked to rate the relevance of the proposed QIs on a 5-point Likert scale (with 1 indicating *Strongly disagree*; 2, *Disagree*; 3, *Neutral*; 4, *Agree*; and 5, *Strongly agree*), including the response option 'cannot assess' if they felt that they did not have the expertise to rate the proposed QI. This response option was not considered in the consensus calculations. Experts were encouraged to elaborate on each of their ratings, propose new QIs and suggest rephrasing of QIs by making use of open-text fields.

A proposed QI was accepted if at least 70% of the experts *Agreed* (Likert score 4) or *Strongly agreed* (Likert score 5) with it. This was a pragmatic decision (indicating that most experts agreed with a proposed QI[44]), but left room for experts to disagree. A proposed QI was rejected if at least 70% of the experts *Strongly disagreed* (Likert score 1) or *Disagreed* (Likert score 2) with it. All consensus scores in between were labelled 'up for discussion'. Responses to the R1 and R3 questionnaires were downloaded in Excel format and analysed descriptively using Microsoft Excel 2016. Only completed written questionnaires were included in the analyses.

The expert panel received both a qualitative feedback report (the provided feedback and comments made for each proposed QI)[37] and a statistical group response[41] for each Delphi round. Each expert was anonymous to the other members of the expert panel. Individual ratings of the proposed QIs were confidential and not shared with other participants. This allowed the experts to express their opinions freely and to avoid dominance.[41]

2.3.1 | Delphi rounds

R1 was open between 7 June and 28 June 2021. Reminders were sent by email after 1 and 2 weeks after the initial invitation. In R1, 38 proposals (four general statements and 34 QIs) were appraised (Table 1).

R2 was held during the EACPT Virtual Meeting on 29 June 2021 and was announced via the official Meeting Programme and by email. All participants invited to attend R1 were again invited to participate in R2. R2 was also open to attendees of the 2021 EACPT Virtual Meeting and was free of charge.

All proposed QIs that were rejected or considered up for discussion in R1 formed the topic guide for R2, to determine why they received low Likert scores. Participants were divided into two separate parallel sessions. Two members of the Steering Committee moderated a parallel session (group A by MvA [male] and KS [female]; group B by JT [male] and RM [female]). In each parallel session, a unique set of proposed QIs was presented, and participants were encouraged to discuss each QI presented or to propose new QIs, either verbally or through written input. Written input was provided anonymously using Google Jamboards.

R2 was audio and video recorded and then transcribed. After transcription, two members of the Steering Committee (RM and JT) independently analysed the data thematically. After evaluation by the Steering Committee, the results of R1 and R2 were presented to the expert panel in R3.

All experts who were either invited or participated in R1 and R2, were invited to participate in R3. This round was open between 4 August 2021 and 22 September 2021. A reminder via email was sent after 4 weeks after the initial invitation.

2.3.2 | Phase 3: Completion phase

Proposed QIs that were rejected or considered up for discussion after R3 were discussed by the Steering Committee, which made the final decision on inclusion/exclusion of these QIs, based on the consensus rate and any comments and arguments provided by the expert panel.

3 | RESULTS

The expert panel rated 59 proposed QIs and four general statements in three Delphi rounds. A total of 183 experts were invited to participate (158 initially selected experts and 25 additional proposed experts), of whom 61 experts (33%) from 23 different countries completed R1. Seventeen experts participated in R2. A total of 194 experts (all 183 experts from R1 and 11 additional proposed experts) were invited to participate in R3, which was completed by 56 experts (29%) from 24 different countries (Figure 2). The characteristics and demographics of the participating experts are presented in Table S5. Of the 61 experts who participated in R1, 11 (18%) also participated in R2. Forty-one experts participated in both R1 and R3 (50.6%), and seven experts (8.6%) completed all three Delphi rounds.

3.1 | Delphi rounds and completion phase

3.1.1 | R1: First questionnaire

All four general statements assessing support for and the need for international consensus on the fundamentals of the Framework were accepted. The consensus rates ranged from 77% to 97% (Table 1, G1–4). Seventeen (50%) QIs were accepted in R1 with a consensus rate of 79%–97% (Table 1, Figure 2). Although QI1 was accepted (95% consensus), it was rephrased to QI35 based on experts' written input but was not discussed in R2 and R3 (Table S6). Fourteen (41%) QIs were considered up for discussion and three (9%) QIs were rejected (consensus 3%–10%). Although QIs 15, 16 and 17 were accepted in R1, the Steering Committee decided to submit them for in-depth discussion during R2 based on written input from the expert panel (Table S6). As a result, 20 QIs were presented for in-depth discussion in R2 (Table 1, QI15–34).

TABLE 1 Overview of proposed, accepted, rejected and discussed quality indicators over all Delphi rounds.

#	Quality indicator	% consensus*	Action	Conclusion
General statements				
G.1	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, a hospital should have a structured in-hospital pharmacotherapeutic stewardship programme.	97%	NA	Accepted in R1
G.2	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, there should be European consensus on the fundamentals of an in-hospital pharmacotherapeutic stewardship programme.	77%	NA	Accepted in R1
G.3	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, each in-hospital setting in Europe should have a pharmacotherapeutic stewardship programme.	82%	NA	Accepted in R1
G.4	If a hospital wants to set up an in-hospital pharmacotherapeutic stewardship programme, a framework should be available that includes evidence-based and applicable quality indicators (QIs).	90%	NA	Accepted in R1
Initially proposed quality indicators				
1	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, there should be a policy that outlines the responsibilities of the people active in an in-hospital pharmacotherapeutic stewardship programme.	95%	Rephrased based on comments in R1 in #35	
2	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, should be tailored to a hospital's specific needs.	92%		Accepted in R1 and included in final set of QIs
3	A pharmacotherapeutic stewardship programme should provide metrics and insight into the status of medication safety in the hospital where it is active.	95%		Accepted in R1 and included in final set of QIs
4	There should be a formal team of healthcare professionals performing the tasks defined in an in-hospital pharmacotherapeutic stewardship programme.	93%		Accepted in R1 and included in final set of QIs
5	The team performing in-hospital pharmacotherapeutic stewardship, and the tasks of this programme should have identifiable and qualified team members who have been allocated time for in-hospital pharmacotherapeutic stewardship in their work schedule.	97%		Accepted in R1 and included in final set of QIs

(Continues)

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
6	The team performing in-hospital pharmacotherapeutic stewardship, and the tasks of this programme should have an identifiable, pharmacological qualified leader who has been allocated time for pharmacotherapeutic stewardship in their work schedule.	97%		Accepted in R1 and included in final set of QIs
7	The team performing in-hospital pharmacotherapeutic stewardship, and the tasks of this programme should monitor quality indicators (QIs) for pharmacotherapeutic stewardship and should make these data available.	97%		Accepted in R1 and included in final set of QIs
8	There should be a system in place for rapid communication between prescribers and team members.	90%		Accepted in R1 and included in final set of QIs
9	There should be a mechanism in place to request pharmacotherapeutic assessment of patients by stakeholders in the hospital.	90%		Accepted in R1 and included in final set of QIs
10	Pharmacotherapeutic assessment should be performed by a competent member of the pharmacotherapy team.	87%		Accepted in R1 and included in final set of QIs
11	Prescribers should be given the opportunity to decline or accept advice given by the team on the basis of its pharmacotherapeutic assessment.	84%		Accepted in R1 and included in final set of QIs
12	The pharmacotherapeutic stewardship plan should be documented in the discharge summary or correspondence to the next line of care.	87%		Accepted in R1 and included in final set of QIs
13	Satisfaction status/experience of patients receiving pharmacotherapeutic stewardship should be monitored.	80%		Accepted in R1 and included in final set of QIs
14	Hospital readmission status of patients receiving in-hospital pharmacotherapeutic stewardship should be documented.	82%		Accepted in R1 and included in final set of QIs
15	There should be a weekly multidisciplinary meeting/ward round (face-to-face/virtual) to discuss findings of patients eligible to receive pharmacotherapeutic stewardship.	79%	Accepted but up for discussion after R1 based on decision Steering Committee	Rephrased after R2 in #36
16	The pharmacotherapeutic stewardship plan should be documented in patient's record.	95%	Accepted but up for discussion after R1 based on decision Steering Committee	Rephrased after R2 in #37

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
17	The team performing in-hospital pharmacotherapeutic stewardship should document …		Accepted but up for discussion after R1 based on decision Steering Committee	Rephrased after R2 in #38
	The number of potentially inappropriate medications (PIMs).	89%		
	Document the number of (preventable) adverse drug events (ADEs).	82%		
	The number of (preventable) adverse drug reactions (ADRs).	89%		
	The number of discrepancies (either intentional or unintentional) between the medication in use before hospitalization and the medication in use at hospital discharge.	84%		
	The number of patients identified with at least one prescribing error (PE).	90%		
	The number of prescribing errors (PEs) identified after pharmacotherapeutic assessment.	92%		
18	A pharmacotherapeutic stewardship programme should at least include the following activities:		Up for discussion after R1	Rephrased after R2 in #39
	Medication reconciliation at hospital admission	79%		
	A face-to-face/virtual medication interview with a patient	46%		
	A structured medication review during patient's hospitalization	75%		
	A structured medication review upon patient's hospital discharge	80%		
	Education for in-hospital prescribers regarding pharmacology and pharmacotherapy	84%		
	Education for nurses regarding pharmacology and pharmacotherapy	72%		
	Medication reconciliation at hospital discharge	72%		
	Monitoring whether the correct dose and formulation of a medication is given when a patient has a nasogastric tube	43%		
	Monitoring that medication is given correctly if a patient is not able to take their medication orally (e.g. in case of [temporarily] problems swallowing medication or having a nasogastric tube)	43%		
	Monitoring and reporting of adverse drug events (ADEs)	87%		

(Continues)

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
	Optimization of local protocols	62%		
	Identification of computerized physician order entry (CPOE) system	39%		
	Other	8%		
19	A pharmacotherapeutic stewardship programme should prioritize activities on clinical wards that provide acute care, for example, the emergency department or acute admission ward.	66%	Up for discussion after R1	Merged with 20 and 21 and rephrased after R2 in #40
20	A pharmacotherapeutic stewardship programme should prioritize activities on non-acute, surgical wards.	48%	Up for discussion after R1	Merged with 19 and 21 and rephrased after R2 in #40
21	A pharmacotherapeutic stewardship programme should prioritize activities on non-acute, medical wards.	56%	Up for discussion after R1	Merged with 19 and 20 and rephrased after R2 in #40
22	A pharmacotherapeutic stewardship programme should focus on all adult (18 years and older) patients.	56%	Up for discussion after R1	Merged with 23, 24 and 25 and rephrased after R2 in #41 & #42
23	A pharmacotherapeutic stewardship programme should only focus on older (65 years and older) patients.	25%	Up for discussion after R1	Merged with 22, 24 and 25 and rephrased after R2 in #41 & #42
24	A pharmacotherapeutic stewardship programme should only focus on patients with polypharmacy (five or more chronic medications in use).	18%	Up for discussion after R1	Merged with 22, 23 and 25 and rephrased after R2 in #41 & #42
25	A pharmacotherapeutic stewardship programme should include all hospitalized patients, regardless of the number of medications in use.	64%	Up for discussion after R1	Merged with 22, 23 and 24 and rephrased after R2 in #41 & #42
26	The team performing in-hospital pharmacotherapeutic stewardship should include at least the following medical specialty/specialties:		Up for discussion after R1	Split and rephrased after R2 in #43 & #44
	Junior medical doctor (0–2 years of experience)	26%		
	Senior medical doctor (at least 2 years of experience)	48%		
	Specialized medical doctor	64%		
	Clinical hospital pharmacist	89%		
	Public pharmacist	5%		
	Physician assistant	13%		
	Nurse	36%		
	Medical student	18%		
	Pharmacy student	16%		
	Pharmacy technician	3%		
	Pharmacy practitioner	11%		
	Nurse practitioner	13%		

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
	Clinical pharmacologist	87%		
	Other	3%		
27	The team performing in-hospital pharmacotherapeutic stewardship and tasks within this programme should ideally include the following medical specialty/ specialties:		Up for discussion after R1	Rephrased after R2 in #45
	Junior medical doctor (0–2 years of experience)	54%		
	Senior medical doctor (at least 2 years of experience)	61%		
	Specialized medical doctor	77%		
	Clinical hospital pharmacist	82%		
	Public pharmacist	20%		
	Physician assistant	26%		
	Nurse	64%		
	Medical student	36%		
	Pharmacy student	34%		
	Pharmacy technician	3%		
	Pharmacy practitioner	15%		
	Nurse practitioner	39%		
	Clinical pharmacologist	95%		
	Other	2%		
28	Patients and their family should be informed about the outcomes of pharmacotherapeutic assessment and resulting decisions.	66%	Up for discussion after R1	Rephrased after R2 in #46
29	Satisfaction status/experience of clinicians consulting the pharmacotherapy team should be monitored.	64%	Up for discussion after R1	Rephrased after R2 in #47
30	Survival status of patients receiving in-hospital pharmacotherapeutic stewardship should be documented.	64%	Up for discussion after R1	Rejected after R2 from final set of QIs
31	The team performing in-hospital pharmacotherapeutic stewardship should document the number of days a patient is inoptimally treated with medication.	67%	Up for discussion after R1	Rejected after R2 from final set of QIs
32	A pharmacotherapeutic stewardship programme should only be active during office hours (i.e. not at the weekend).	8%	Up for discussion after R1	Merged with #33 after R2 and rephrased in #48
33	A pharmacotherapeutic stewardship programme should only be active after office hours and during the weekends (i.e. not during office hours).	10%	Up for discussion after R1	Merged with 32 after R2 and rephrased in #48

(Continues)

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
34	A pharmacotherapeutic stewardship programme should have a more reactive (passive) approach, rather than a proactive (active) approach.	3%	Up for discussion after R1	Rephrased after R2 in #49
Rephrased quality indicators after R1 and/or R2				
35	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, there should be a policy that outlines the tasks of the people active in an in-hospital pharmacotherapeutic stewardship programme.	N.A.		Accepted in R1 and included in final set of QIs
36	There should be a face-to-face (virtual) meeting(s) with the physician(s) clinically responsible, to discuss real-time findings of patients receiving pharmacotherapeutic stewardship.	82%		Accepted in R3 and included in final set of QIs
37	The pharmacotherapeutic stewardship plan should be documented in a patient's record and signed by physician clinically responsible for the patient (shared responsibility).	84%		Accepted in R3 and included in final set of QIs
38	The team performing in-hospital pharmacotherapeutic stewardship should document outcome measures that are appropriate and feasible for the outcome defined within that hospital (e.g. the number of potentially inappropriate medications (PIMs); the number of (preventable) adverse drug events (ADEs); the number of (preventable) adverse drug reactions (ADRs); the number of discrepancies (either intentional or unintentional) between the medication in use in before hospitalization and the medication in use at hospital discharge; the number of patients identified with at least one prescribing error (PE); the number of prescribing errors (PEs) identified after pharmacotherapeutic assessment).	84%		Accepted in R3 and included in final set of QIs
39	Activities of a pharmacotherapeutic stewardship programme should at least include medication reconciliation at hospital admission; a structured medication review during patient's hospitalization; a structured medication review upon patient's hospital discharge; education for in-hospital prescribers and nurses regarding pharmacology and pharmacotherapy; medication reconciliation at hospital discharge; and surveillance on and reporting of adverse drug events (ADEs).	91%		Accepted in R3 and included in final set of QIs

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
40	A pharmacotherapeutic stewardship programme should be active throughout the whole in-hospital setting regardless of the ward (acute, non-acute, medical, surgical, paediatrics).	79%		Accepted in R3 and included in final set of QIs
41	The team performing in-hospital pharmacotherapeutic stewardship should prioritize activities on high-risk wards and support high-risk medical specialties based on risk assessment of the outcome defined for the hospital's pharmacotherapeutic stewardship programme.	89%		Accepted in R3 and included in final set of QIs
42	A pharmacotherapeutic stewardship programme should include all hospitalized patients, regardless of the number of medications in use or age.	60%	Up for discussion for Steering Committee	Rejected after R3 from final set of QIs
43	The team performing in-hospital pharmacotherapeutic stewardship should consist of a core team.	88%		Accepted in R3 and included in final set of QIs
44	The team performing in-hospital pharmacotherapeutic stewardship should at least include a senior medical specialist, preferably with a specialization in clinical pharmacology and a clinical/hospital pharmacist.	96%		Accepted in R3 and included in final set of QIs
45	There should be an opportunity to extend the team performing in-hospital pharmacotherapeutic stewardship with dynamic team members (e.g. a nurse, junior doctor, clinical pharmacologists), for example, for training purposes.	91%		Accepted in R3 and included in final set of QIs
46	Patients and their family should be informed about the outcomes of pharmacotherapeutic assessment and resulting decisions by the clinically responsible physician.	68%	Up for discussion for Steering Committee	Rejected after R3 from final set of QIs
47	Satisfaction status/experience of clinicians should be monitored with a view to improving the pharmacotherapeutic stewardship programme and team (in a continuous cycle).	89%		Accepted in R3 and included in final set of QIs
48	A pharmacotherapeutic stewardship programme should be active 24/7, meaning not only during office hours or only outside office hours. It is possible, depending on a hospital's needs, for specific activities of the in-hospital pharmacotherapeutic stewardship programme to be active or nonactive at specific moments of the day or week.	57%	Up for discussion for Steering Committee	Rejected after R3 from final set of QIs

(Continues)

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
49	A pharmacotherapeutic stewardship programme should include both a proactive (active) approach and a reactive (passive) approach depending on the specific activity of the in-hospital pharmacotherapeutic stewardship programme, hospital's needs and resources.	89%		Accepted in R3 and included in final set of QIs
Newly proposed quality indicators after R1 and/or R2				
50	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, pharmacotherapeutic stewardship is essential when there are multiple prescribers involved with a patient.	93%		Accepted in R3 and included in final set of QIs
51	A pharmacotherapeutic stewardship programme should aim to reduce and prevent prescribing errors emerging at different moments of the in-hospital prescribing process.	96%		Accepted in R3 and included in final set of QIs
52	A pharmacotherapeutic stewardship programme should include multiple, different activities relevant to its aim.	89%		Accepted in R3 and included in final set of QIs
53	The outcome of a pharmacotherapeutic stewardship programme should be determined and clearly defined by the hospital where the programme is active in.	89%		Accepted in R3 and included in final set of QIs
54	The research outcome(s) of a pharmacotherapeutic stewardship programme should be distinct from the outcome(s) of daily clinical practice.	52%	Up for discussion for Steering Committee	Rejected after R3 from final set of QIs
55	The activities of a pharmacotherapeutic stewardship programme should be tailored to a hospital's specific needs and available resources.	84%		Accepted in R3 and included in final set of QIs
56	The activities of a hospital's pharmacotherapeutic stewardship programme should be prioritized based on individual patient's risk concerning medication safety.	89%		Accepted in R3 and included in final set of QIs
57	The team performing in-hospital pharmacotherapeutic stewardship should support prescribers by providing guidance and advice instead of taking over the prescribing task.	95%		Accepted in R3 and included in final set of QIs
58	The frequency of face-to-face (virtual) a meeting(s) with the physician clinically responsible should be dependent of the needs and turnover of patients.	84%		Accepted in R3 and included in final set of QIs

TABLE 1 (Continued)

#	Quality indicator	% consensus*	Action	Conclusion
59	Outcome measures should be appropriate and supportive of the defined outcome of a hospital's pharmacotherapeutic stewardship programme.	88%		Accepted in R3 and included in final set of QIs
60	The efficacy of a pharmacotherapeutic stewardship programme should be assessed with regard to hospital procedures and patient outcomes, using separate and appropriate outcome measures.	84%		Accepted in R3 and included in final set of QIs

Abbreviations: N.A., not applicable; R1, first Delphi round; R2, second Delphi round; R3, third Delphi round.

3.1.2 | R2: Focus meeting

Twenty QIs from R1 were discussed in two parallel groups (nine experts in group A and eight in group B) during a 90-minute virtual focus meeting. The output of each parallel session was made available for discussion by all attendees.

Following the analyses of R2, the Steering Committee decided to reject two QIs from R1 (Table 1, QI30 and QI31) based on the expert panel's arguments that they were labour intensive and therefore not hands-on. After R2, the 18 remaining QIs were split or merged with other proposed QIs, resulting in 14 rephrased QIs (Table 1, QI36–QI49). In addition, 11 new QIs emerged during this round (Table 1, QI50–QI60). These 25 QIs were presented for rating in R3.

3.1.3 | R3: Second questionnaire

Twenty-five QIs (Table 1, QI36–QI60) were presented to the expert panel: consensus was reached on 21 proposed QIs (84%), and four were considered 'up for discussion'. None were rejected (Table 1). The Steering Committee rejected the four QIs considered up for discussion, mainly due to lack of consensus in the expert panel. Therefore, 35 QIs were included in the final set, forming the framework of IPS (Table 2).

3.2 | The framework of in-hospital pharmacotherapeutic stewardship

3.2.1 | Structure

The expert panel agreed that there should be a formal team of healthcare professionals performing the tasks of an IPS programme (93% consensus), and that team members should be identifiable, qualified and be allocated time in their work schedules to perform these tasks (97% consensus). "Otherwise, it could be imagined that, for example, a medical specialist would spend all their time on daily clinical tasks", the experts argued.

The composition of the IPS team was discussed extensively, with emphasis on its multidisciplinary nature. This was because the experts felt that the different backgrounds and expertise of the team members would promote interprofessional collaboration and synergy, which would be beneficial in reducing in-hospital PEs, although it was recognised that the type of hospital would also be a determinant. For example, one expert argued: "In an academic hospital, students are always available. However, not every hospital has students on a regular basis, let alone that they will have time to participate and contribute to this team". After three Delphi rounds, the expert panel agreed that the team delivering IPS should consist of 'a core team' (88% consensus) with the possibility of including additional team members as needed (e.g. a nurse, junior doctor, clinical pharmacologists), for example, for training purposes (91% consensus). This would allow hospitals to build a team based on availability and resources. The expert panel

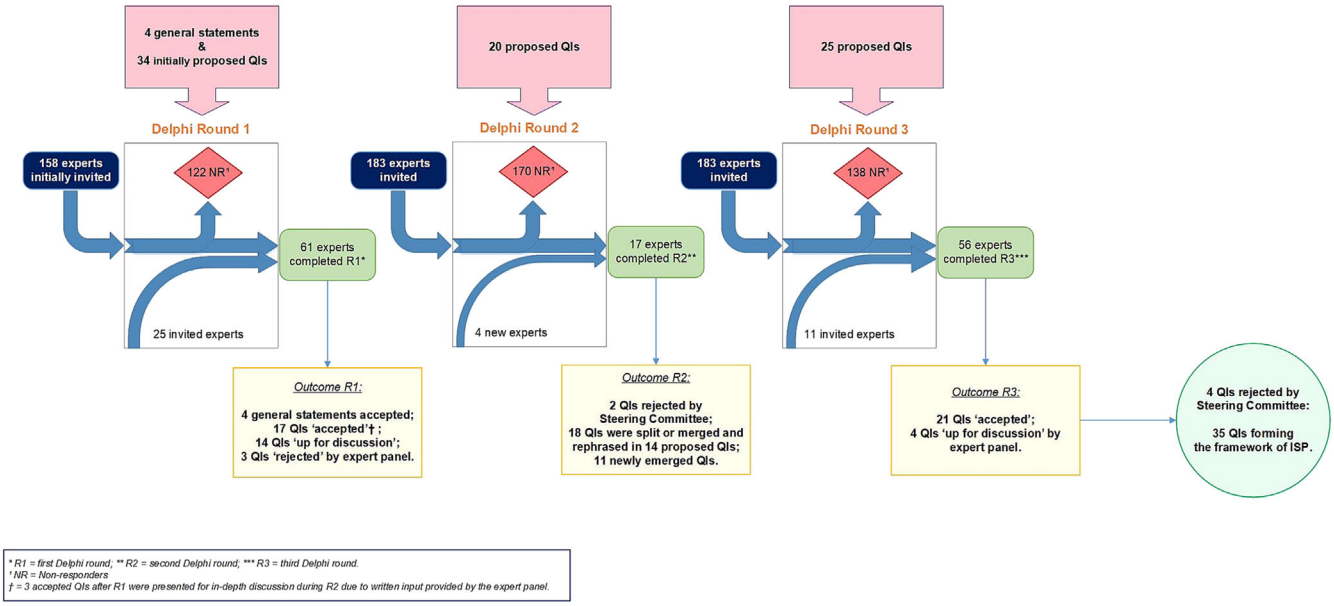

FIGURE 2 Overview of the participants and QIs over the three Delphi rounds.

agreed (96%) that the IPS team should include at least a senior medical specialist, preferably with a specialisation in clinical pharmacology, and a clinical/hospital pharmacist.

The expert panel concluded that an IPS programme should include several activities (89% consensus), because multiple factors influence the occurrence of in-hospital PEs. PEs can emerge in different stages of hospitalisation, for example, at admission, discharge and during intramural transfers.

The expert panel recognised that, although not all in-hospital settings have the same challenges or preventive barriers regarding PEs, it was important to define QIs covering the activities and tasks of an IPS team that could be generalisable and applied internationally. Therefore, the expert panel agreed that the activities and tasks of an IPS programme should be tailored to a hospital's specific needs and the resources available (84% consensus). However, in order benchmark a level of uniformity between (international) IPS programmes, it was agreed that some activities should be mandatory, namely, medication reconciliation at hospital admission and discharge; a structured medication review during a patient's hospital stay and at discharge; education of hospital prescribers and nurses on pharmacology and pharmacotherapy; and surveillance on and reporting of adverse drug events (91% consensus; Table 2).

3.2.2 | Process

Consensus was reached on the communication and collaboration characteristics of the IPS team and the high-risk situations in which pharmacotherapeutic stewardship would be necessary.

The expert panel argued that the prescriber acceptance of an IPS team and its efficacy could only be ensured if the team focused on, and invested time in, establishing good collaboration with in-hospital prescribers. The IPS team should support prescribers by providing guidance and advice - it should not take over the prescribing task (95% consensus). In addition, prescribers should be allowed to decline the advice given based on a pharmacotherapeutic assessment of the IPS team (84% consensus). This should preferably be done in a face-to-face (virtual) meeting(s), to allow discussion of IPS findings (82% consensus). The IPS plan should be recorded in the patient's medical record and signed by the clinician responsible for the patient, thus promoting shared responsibility (84% consensus). Finally, the IPS plan, and the underlying rationale for recommending a specific post-hospitalisation treatment plan should be documented in the discharge summary or correspondence to the next line of care (87% consensus), to ensure continuity of care.

An issue that generated discussion in all three Delphi rounds was whether, and how, patients should be stratified (high risk, low risk, etc.). It was agreed that it was necessary to define high-risk patients because in daily clinical practice there is not enough time to review the medication lists of all inpatients, regardless of age and medication use, without some form of risk stratification. The definition of 'high risk' was identified as a challenge in the R2 discussions. For example, in the literature and in daily practice, patients on polypharmacy are often labelled as high-risk, based on the assumption that the higher the number of medications used, the higher the risk of a PE. However, it has been pointed out that with this definition excludes patients with no or few medications or those who are non-adherent to medication, even though they may benefit from IPS. Furthermore, experts argued that IPS is essential when multiple prescribers are involved with a single patient. Experts agreed that IPS should not be limited to specific clinical wards (acute, non-acute, medical, surgical, paediatric) or specific medical specialties, such as surgery. Instead, experts argued that

TABLE 2 Final set of quality indicators for in-hospital pharmacotherapeutic stewardship obtained in international consensus programme.

#	Quality indicator	% consensus*
Structure		
General		
1	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, an in-hospital pharmacotherapeutic stewardship programme should be tailored to a hospital's specific needs.	92%
2	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, there should be a policy that outlines the tasks of people active in an in-hospital pharmacotherapeutic stewardship programme.	95%
The team performing in-hospital pharmacotherapeutic stewardship (IPS)		
3	There should be a formal team of healthcare professionals performing the tasks defined in an in-hospital pharmacotherapeutic stewardship programme.	93%
4	The team should have identifiable and qualified team members and should have time allocated to the performance of these tasks in their work schedule.	97%
5	The team should at least consist of a core team.	88%
6	The team should at least include a senior medical specialist, preferably with a specialization in clinical pharmacology and a clinical/hospital pharmacist.	96%
7	There should be an opportunity to extend the team with other members (e.g. a nurse, junior doctor, clinical pharmacologists), for example, for training purposes.	91%
8	The team should have an identifiable, pharmacological qualified lead team member whose work schedule allocates time for this task.	97%
Communication		
9	There should be a system in place for rapid communication between prescribers and IPS team members.	90%
10	There should be a mechanism in place to request pharmacotherapeutic assessment of patients by the IPS team by stakeholders in the hospital.	90%
Activities and tasks		
11	An IPS programme should include multiple, different activities to pursue its aim.	89%
12	Activities of an IPS programme should at least include: medication reconciliation at hospital admission; a structured medication review during patient's hospitalization; a structured medication review upon patient's hospital discharge; education for in-hospital prescribers and nurses regarding pharmacology and pharmacotherapy; medication reconciliation at hospital discharge; and surveillance on and reporting of adverse drug events (ADEs).	91%
13	A pharmacotherapeutic stewardship programme should aim to reduce and prevent prescribing errors that occur at different moments of the in-hospital prescribing process.	96%
14	Activities of an IPS programme should be tailored to a hospital's specific needs and available resources.	84%

(Continues)

TABLE 2 (Continued)

#	Quality indicator	% consensus*
15	A pharmacotherapeutic stewardship programme should provide metrics and insight into the status of medication safety in the hospital where it is active.	95%
16	The team performing IPS should monitor quality indicators (QIs) for pharmacotherapeutic stewardship and should make these data available.	97%
17	Pharmacotherapeutic assessment should be performed by a competent member of the pharmacotherapeutic stewardship team.	87%
Process		
Communication and collaboration		
18	The pharmacotherapeutic stewardship plan should be documented in the discharge summary or correspondence to the next line of care.	87%
19	The pharmacotherapeutic stewardship plan should be documented in the patient's record and signed by physician clinically responsible for the patient (shared responsibility).	84%
20	There should be a face-to-face (virtual) a meeting(s) with physician clinically responsible, to discuss real-time findings of patients receiving IPS.	82%
21	The frequency of face-to-face (virtual) a meeting(s) with physician clinically responsible should be dependent of the needs and turnover of patients.	84%
22	The IPS team should support prescribers by providing guidance and advice instead of taking over the prescribing task.	95%
23	Prescribers should be given the opportunity to decline or accept advice given by the IPS team.	84%
High-risk situations		
24	An IPS programme should be active throughout the whole in-hospital setting regardless of the ward (acute, non-acute, medical, surgical, paediatrics).	79%
25	The IPS team should prioritize activities on high-risk wards and support high-risk medical specialties, based on risk assessment of the outcome given in the hospital's pharmacotherapeutic stewardship programme.	89%
26	The activities of a hospital's IPS programme should be prioritized based on an individual patient risk concerning medication safety.	89%
27	An IPS programme should include both a proactive (active) approach and a reactive (passive) approach depending on the specific activity of the in-hospital pharmacotherapeutic stewardship programme and the hospital's needs and resources.	89%
28	To enable safe, effective and high-quality in-hospital pharmacotherapeutic care, pharmacotherapeutic stewardship is essential when multiple prescribers are involved in the care of the same patient.	93%
Outcome		
General		
29	The outcome of a pharmacotherapeutic stewardship programme should be determined and clearly defined by the hospital involved.	89%

TABLE 2 (Continued)

#	Quality indicator	% consensus*
30	Outcome measures should be appropriate and supportive of the outcomes defined in a hospital's pharmacotherapeutic stewardship programme.	88%
31	The efficacy of a pharmacotherapeutic stewardship programme should be assessed at the level of hospital procedures and patient care, using appropriate outcome measures.	84%
Core outcomes		
32	The team performing in-hospital pharmacotherapeutic stewardship should document outcome measures that are appropriate and feasible for defined outcomes: e.g. the number of potentially inappropriate medications (PIMs); the number of (preventable) adverse drug events (ADEs); the number of (preventable) adverse drug reactions (ADRs); the number of discrepancies (either intentional or unintentional) between the medication in use in before hospitalization and the medication in use at hospital discharge; the number of patients identified with at least one prescribing error (PE); the number of prescribing errors (PEs) identified after pharmacotherapeutic assessment.	84%
33	Satisfaction status/experience of patients receiving pharmacotherapeutic stewardship should be monitored.	80%
34	Satisfaction status/experience of clinicians should be monitored with a view to improving, and collaboration in, the pharmacotherapeutic stewardship programme and team (in a continuous cycle).	89%
35	Hospital readmission status of patients receiving in-hospital pharmacotherapeutic stewardship should be documented.	82%

an IPS team should identify high-risk wards based on a risk assessment, and prioritise activities and support for these specific wards, implying a tailored rather than a one-size-fits-all approach.

After three Delphi rounds, the expert panel agreed that stratification based on high-risk patients was necessary to ensure feasible and appropriate care, rejecting the idea that all hospitalised patients should be eligable, regardless of the number of medications in use or the patient's age. However, there was no consensus on the characteristics of patients eligible for IPS.

3.2.3 | Outcome

Selecting appropriate outcome measures for IPS programmes has been challenging from an international perspective. The recommended outcome measures should be inclusive, independent of how healthcare is organised and tailorable to the setting's specific needs. Outcome measures should not only be appropriate but also feasible for a given hospital setting and resources. Six appropriate core outcomes were selected: the number of potentially inappropriate medications (PIMs); the number of (preventable) adverse drug events (ADEs); the number of (preventable) adverse drug reactions (ADRs); the number of discrepancies (eg the drug, the dosage, the frequency, the form, the time or day of administration) (either intentional or unintentional) between medication use before hospital admission and at the time of discharge; the number of patients identified with at least one prescribing error (PE); the number of prescribing errors (PEs) identified after pharmacotherapeutic assessment (84% consensus; Table 2). These six core outcomes allows IPS programmes to be compared internationally, thereby facilitating appropriate monitoring of the prevalence, incidence and cost of in-hospital PEs at a European level.

4 | DISCUSSION

This study used a Delphi procedure to develop a set of QIs to form the basis of an IPS programme. At the same time, we assessed the need for and support of this novel approach to reducing prescribing

errors among an international expert panel of clinical pharmacologists, medical doctors and pharmacists associated with the European Association of Clinical Pharmacology and Therapeutics.

Our set of QIs describes a clear framework for IPS. Significant findings are the consensus reached on a number of issues: a multidisciplinary 'core team' including a senior medical specialist, preferably specialised in clinical pharmacology, and a clinical/hospital pharmacist, plus additional team members as required; the activities and tasks the IPS team should perform to reduce in-hospital PEs; and appropriate outcome measures to evaluate the quality of care provided through IPS. We did not prioritise the QIs agreed upon, in contrast with similar studies concerning outpatient parenteral antimicrobial therapy (OPAT) and antimicrobial stewardship.[44,45] These studies argue that the prioritisation of QIs determines the first goals to accomplish, advocating a 'one size fits all' approach. However, our previous studies show that in-hospital PEs are caused by a variety of factors and can vary between settings,[31,32] which means that measures to reduce PEs need to be tailored to the local in-hospital situation. As argued by the international expert panel, the selected QIs need to be generic to ensure inclusivity and empower the autonomy of local settings, which would make it feasible to set up IPS programmes for different settings. In addition, the QIs can be used to identify, prioritize and evaluate PE-reducing activities in different settings.

Intervention studies described in the literature that aim to reduce in-hospital PEs do not clearly describe 'how work is done' in daily local practice[24–26,30,46–51] and therefore do not provide a Safety-II—perspective.[52] This hampers objective evaluation of the actual impact of such interventions and the generalisability of the intervention and its effect in other settings. This may explain why there is an abundance of studies conducted on how to reduce PEs, even though the number of PEs is not decreasing at a global level. The set of QIs selected in this study, with their clear identification of who does what, will allow researchers to determine whether strategies to reduce PEs are effective in their setting. This in turn will allow the effects of different strategies to reduce PEs to be compared in other hospital settings, hopefully leading to a reduction in in-hospital PEs internationally.

4.1 | Strengths and limitations

Our study had several major strengths. First, the set of QIs was developed using two literature searches. It involved the input of an international, multidisciplinary expert panel representing specialists in clinical pharmacology, including medical doctors and pharmacists with varying levels of professional experience, and representing most European countries. This expert panel provided diverse points of view and opinions in support of the validity of the framework. Secondly, the consensus rate per accepted QI and general statement was higher than the pragmatically chosen cut-off of 70%. These results demonstrate the support and need for international consensus on the fundamentals of this novel concept aiming to circumvent in-hospital PEs.

Our study also had some limitations. As this was the first and essential step in establishing the framework for IPS, we surveyed a specific group of experts, namely, clinical pharmacologists, who have the knowledge and expertise in the safe, rational, effective and economical use of drugs.[53] Other stakeholders were not invited to participate in our expert panels, such as medical specialties requesting IPS, hospital board members of hospitals or patients potentially eligible for IPS. Their views would be valuable, for example in examining potential barriers to the implementation of IPS. It was beyond the scope of this article to include these stakeholders, but they should be included in future studies. Nevertheless, we consider it a strength that this multidisciplinary group of medical specialists concerned with the safe, rational, effective and economical use of drugs supported the concept of IPS and were willing to contribute to its development. Finally, most of our experts were from European countries. This may limit the generalisability of the study results to countries outside Europe. Interesting future steps would be to determine the acceptance, applicability and implementation of this set of QIs in other continents.

4.2 | Future considerations and research

The establishment of a set of QIs that form the framework for IPS is an important first step towards reducing in-hospital PEs and associated harm at an international level, starting with Europe. As mentioned above, future studies should include other relevant stakeholders in addition to clinical pharmacologists to explore potential barriers to the implementation of IPS. In the current study, no consensus was reached on which patients should (at least) be targeted by IPS due to their risk of medication-related harm. Our findings support those of the recent systematic review by Deawjaroen et al.[54] The authors identified 14 currently available prediction tools and assessed their clinical utility in identifying adult hospitalised patients at risk of medication-related harm. Interestingly, the authors concluded that none of the tools were optimal for this purpose. Therefore, if stratification of "high-risk patients" is needed to allocate the efforts of an IPS team, future studies should approach 'high-risk patients' from a perspective other than the traditional risk factors such as an advanced age, the number of medications used, admission to specific clinical wards or treatment by specific medical specialties, or the use of high-risk medications such as nonsteroidal anti-inflammatory drugs and opioids,[24,55–59] which are included in current stratification strategies.[60,61] Finally, future research should be conducted to assess whether IPS improves in-hospital medication safety in daily practice by reducing in-hospital PEs and associated harms. To this end, the six outcome measures that were agreed to be appropriate for IPS in this study should be used to determine and monitor the prevalence and incidence of in-hospital PEs with IPS and its cost-effectiveness.

5 | CONCLUSION

A critical first, international step has been taken to introduce a novel approach, IPS, to address the complex challenge of reducing the

number of in-hospital PEs. An international panel of experts agreed on a set of 35 QIs covering the domains 'Structure', 'Process' and 'Outcome' to guide and evaluate the quality of care provided with IPS. These QIs may help hospitals intending to set up an in-hospital IPS programme to reduce in-hospital PEs.

AUTHOR CONTRIBUTIONS

Rashudy F. Mahomedradja, Jelle Tichelaar, Kim C.E. Sigaloff and Michiel A. van Agtmael were responsible for study conception and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; and critical revision: Lidwine B. Mokkink was responsible for study conception and design; drafting of manuscript; and critical revision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Rashudy F. Mahomedradja https://orcid.org/0000-0002-8495-6231

Michiel A. van Agtmael https://orcid.org/0000-0002-7966-6934

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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