

Quality indicators as a tool in improving the introduction of new medicines

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Abstract

Introduction: Quality indicators are increasingly used as a tool to achieve safe and quality clinical care, cost-effective therapy, for professional learning, remuneration, accreditation and financial incentives. A substantial number focus on drug therapy but few address the introduction of new medicines even though this is a burning issue. **Objective:** Describe the issues and challenges in designing and implementing a transparent indicator framework and evaluation protocol for the introduction of new medicines and to provide guidance on how to apply quality indicators in the managed entry of new medicines. **Results:** Quality indicators need to be developed early to assess whether new medicines are introduced appropriately. A number of key factors need to be addressed when developing, applying and evaluating indicators including dimensions of quality, suggested testing protocols, potential data sources, key implementation factors such as intended and unintended consequences, budget impact and cost-effectiveness, assuring the involvement of medical professions, patients and the public, and reliable and easy-to-use computerised tools for data collection and management. Transparent approaches include the need for any quality indicators developed to handle conflicts of interests to enhance their validity and acceptance. **Conclusion:** The suggested framework and indicator testing protocol may be useful in assessing the applicability of indicators for new medicines and may be adapted to health care settings worldwide. The suggestions build on existing literature to create a field testing methodology that can be used to produce country specific quality indicators for new medicines as well as a pan-international approach to facilitate access to new medicines.

Introduction

Drug therapy and vaccines play an important role in prevention and treatment of many diseases. During the last decades, new drugs and vaccines have markedly decreased mortality and hospital care and have improved the quality of life for millions of people in lower income as well as in higher income countries¹. However, if these drugs and vaccines are used improperly, the negative or unintended consequences can outweigh their benefits. In some cases, inappropriate use may result simply in the absence of any clinical effect or result in a similar clinical effect but at a greater cost; however, there is also potential for increased morbidity and mortality²⁻⁵. The consequences can be costly such as adverse drug reactions (ADRs) in particular in older people and in those with multiple chronic conditions, adding to the costs of healthcare by increasing hospital admissions.⁴⁻⁶ There is however a recognised efficacy-effectiveness gap due to the variation/uncertainty about efficacy and safety when new medicines are introduced.⁷

The introduction of new medicines challenges the ability of European countries to meet Article 3 of the European Convention on Human Rights and Biomedicine⁸, in terms of being able to provide equitable and comprehensive healthcare.⁸⁻¹² This is because pharmaceutical expenditure has been growing by 50% in real terms during the past decade¹³ and this increase is already leading to new premium priced drugs not being funded in some countries.^{9,14} Consequently, the appropriate and safe use of new medicines needs to be introduced with a clear plan both before and after market authorisation to optimise their real world use. This can be undertaken using proposed models centred on the three pillars of pre-, peri- and post-

launch activities aiming for transparency about medical needs, drug use and involving all key stakeholder groups.^{9,11,12}

Quality indicators are used increasingly for benchmarking, as an auditing tool, or to measure the effect of interventions.¹⁵⁻²⁰ Many indicators integrate drug therapy with other aspects of quality of care or link to a procedure such as changes to treatment.^{21,22} Initiatives have also been taken to develop specific indicators focusing on the rational use of medicines¹⁵ particularly for the treatment of common diseases^{15, 22,23} as well as patient safety.²⁴ Corresponding initiatives for medicines introduced in specialist care have been lacking despite the rapid changes in the drug market, with more and more new biologic drugs being introduced for the treatment of cancer and autoimmune diseases.^{5,25-27}

There are various types of indicators with different requirements and purposes.²⁸⁻³⁹ They are important embed in the definition of rational use of medicines as a goal in quality of medicines use, which is “*patients receive medication appropriate to their medical needs, in doses meeting their own individual requirements, for an adequate period of time and at the lowest cost to them and to the community*”.^{11,12} Consequently, effective management of costs is also included in high quality of medicines use.

Indicators designed to assess quality should adhere to a clear definition of quality of care and include key measurement attributes³⁰⁻³⁴ with an *a priori* clear definition and purpose for use. They must be integrated within implementation and quality improvement programmes³⁵ and specific to the appropriate level of the health care system i.e. micro, meso or macro³⁶⁻³⁷ and be related to structure, process or outcome^{15,30,31}

Indicators may be valuable tools in the managed introduction of new medicines. A distinction is needed between using quality indicators as part of a testing protocol or as part of an overall management plan, which is implemented to accompany the introduction of new medicines. The aim of this paper is to describe the issues and challenges in designing and implementing an indicator framework and evaluation protocol for the introduction of new medicines in ambulatory and specialist/hospital care settings, which we believe will be potentially useful in European healthcare systems.

Key issues when introducing new medicines

When introducing new premium priced medicines that improve the health of patients, models are essential to optimise their cost-effective prescribing. Concerns include the potential budget impact, safety and/or effectiveness when the new medicine is used in populations other than those studied in randomised clinical trials^{4,7,9-11,38-42}. This is because whilst only a limited number of new medicines are truly innovative, there is a need to fund these at premium prices in patient populations where they provide greatest value to address the considerable areas of unmet need that still exist in Europe and globally⁴²⁻⁴⁵. Otherwise typically reimbursed at lower prices than current standards^{12,38}. Deliberations on these concerns led to a proposed model to optimise the managed entry of new drugs pre-, peri- and post launch^{9,11,38,42}. Proposed activities range from early warning systems pre-launch to monitoring physician prescribing post-launch.

Key issues affecting the value of new medicines pre- to peri-launch include the weak evidence based on the published literature, a mismatch between efficacy and effectiveness (expectations from clinical trials), limited data available in the public domain, conflicting

views between stakeholders (e.g. on how rapidly drugs should be introduced), the lack of guidelines or other recommendations for comparison, difficulties in setting target levels for treatment and commonly the small number of patients involved in trials.^{7,9-11} A systems level approach is required within a framework that addresses issues relating to the structure-process-outcome building on the suggested model for introducing new medicines.^{9,11,36,37} A number of measures have been introduced to influence drug utilization post-launch. These include prescribing guidelines, cross-disciplinary quality work by physicians including continuous education organized by Drug and Therapeutics Committees, monitoring of prescribing, physician financial incentive schemes and prescribing restrictions^{9,18,38,39,41}. Prescribing restrictions can include prior authorisation by the health authority else 100% co-payment³⁸. Such demand-side measures have been collated under the “4 Es,” i.e., education, engineering, economics and enforcement^{16,38,39}. While these measures and approaches are well developed, the assessment of their impact needs further investigation when applying these to the introduction of new medicines.

Indicators must address the timeline of pre-launch, launch and post launch activities for new medicines. For example, structure indicators defining and forecasting the capacity of the health system to handle the new drug should be developed before the new drug is available on the market especially where there are uncertainties regarding its clinical value, and to provide pertinent information to patients^{5,9,41,42}. Without such initiatives, new medicines may struggle for funding^{41,42}.

Suggested indicators for new medicines

Suggested indicators for the rational introduction of new medicines can be classified using the framework for assessing quality: structure, process and outcome (Table 1)^{15,30} and be grouped, depending on the included clinical information, into drug-specific, disease-specific and patient specific indicators.

Table 1. Dimensions of quality in applicable for drug utilization studies. Developed from Campbell et al 2000 ³¹

STRUCTURES		
<i>Domain</i>	<i>Dimension</i>	<i>Examples or areas where quality indicators could be developed</i>
Physical characteristics	Resources	Financial, personnel, buildings, equipment, availability of information, clinical data and registries
	Organisation of resources	Provider continuity, organization of prescribing and supply of medicines
	Management	Administration; operational and strategic management to support rational drug prescribing, e.g. Drug and Therapeutics Committees
Workforce characteristics	Skill-mix	Skills/knowledge of staff
	Teamworking	Team functioning; Delegation, role in promoting quality of medicines use
Systems characteristics	Engineering activities	Organizational or managerial interventions such as prescribing targets, price: volume agreements
	Educational activities	Extent and nature of prescribing guidance. These may range from simple distribution of printed material to more intensive strategies such as educational outreach visits by trained facilitators.
	Economic interventions	Patient co-payment including tier levels, positive and negative financial incentives and budgets for physicians and pharmacists
	Enforcement	Regulations by law and prescribing restrictions for physicians for new medicines
PROCESSES		
<i>Domain</i>	<i>Dimension</i>	<i>Examples or areas where quality indicators could be developed</i>
Clinical care -acute -chronic -preventive		History taking incl. medication history; relevant measures taken (e.g. lab test) when initiating drug treatment, appropriate drug prescribing, medicines reconciliation
Inter-personal aspects of care		Information exchange/ Communication with patients, patient adherence and persistence
OUTCOME		
<i>Domain</i>	<i>Dimension</i>	<i>Examples or areas where quality indicators could be developed</i>
Health status	Freedom from disease, comfort, longevity	Functional status, symptom relief, quality of Life Year. May include both positive effects of the drug therapy and negative consequences such as hospitalizations and adverse events.
User evaluation	HRQOL	Satisfaction Communication, Self-esteem
Systems	Efficiency, efficacy and equity	May include patient outcome at a population level but also outcome of interventions to promote rational use of drugs

* Activities to promote quality of prescribing. These have been categorized using the four Es': Education, Engineering, Economics and Enforcement (Wettermark et al 2009) ¹⁶.

a) Structure indicators

Indicators describe the structure, capacities and resources needed in a health system for monitoring the managed introduction and follow up of new medicines. Examples of such indicators include:

- Structured process for horizon scanning in place pre-launch. Horizon scanning refers to early warning systems for forecasting drug utilization and expenditure²⁵ and seeks to examine the potential impact on patient care of new medicines that are expected to receive marketing authorisation and their potential threats, opportunities and likely future developments. It is important for initiating research or to forecast best practice
- Access to competence in Health Technology Assessment/evidence based medicine - to assess the value of new therapies pre- to peri-launch
- Proportion of target physicians who have received education around the new therapy pre- to peri-launch
- Proportion of clinics that have implemented a structured protocol to monitor the prescribing of the new medicine
- Proportion of all new drugs launched during the year for which the Drugs and Therapeutics Committee (or other relevant stakeholder) has issued guidelines/ recommendations for their use
- Incentives for quality assessment in routine clinical care of new medicines
- Price: volume agreements or other managed entry arrangements in place to reduce the uncertainty around the budget impact of new premium priced medicines^{46,47}.
- Structure to facilitate interaction and dialogue between relevant health professionals i.e. physicians and pharmacists

b) Process indicators – drug specific with aggregated data

Diffusion patterns of new medicines may be assessed using readily available aggregate sales data. The uptake of new medicines should be compared with existing alternatives, stratified by age, gender, diagnosis and geography⁴⁸. Without patient identity data, the number of DDDs/1000 inhabitants/day (DDD/ TID DDDs = defined daily doses defined as ‘the average maintenance dose of a drug when used in its major indication in adults’⁴⁹) or DDDs/100 bed-days can be used as an estimate of the proportion of the population exposed to the new medicines⁴⁹. However, they are only applicable if there is only one indication (and one DDD) for the new medicine.

Examples of such indicators include:

- The proportion of a new drug in a pharmacological group (% DDD or expenditure), e.g.: proportion of DPP-IV inhibitors (A) as a % of all oral antidiabetic drugs (B) (A/B *100). (Dipeptidyl peptidase-4 inhibitors [DPP-4 inhibitor] – is a vegetarian enzyme formulation with dipeptidyl peptidase IV)⁵⁰
- The overall volume of new medicines in a geographical area, e.g., volume of fingolimod (DDD/ TID) where the treatment of multiple sclerosis is the only approved indication

These may also include monitoring of drug therapies with patient identity data, i.e.:

- Proportion of patients initiated on the anti-arrythmic drug dronedarone for whom liver function is controlled – (Dronedarone is a antiarrhythmic agent pharmacologically related to amiodarone but developed to reduce the risk of side effects⁵¹)
- Proportion of patients with HIV tested for CCR5-tropic HIV prior to being prescribed maraviroc⁵

- Proportion of patients initiated on an angiotensin receptor blocker (ARB) having previously been treated with an angiotensin enzyme converting inhibitor (ACEI) ⁵²
- Proportion of elderly patients initiated on the oral anticoagulant drug dabigatran for whom their renal function is assessed before starting therapy ^{9,41,42}
- Proportion of patients initiated on a new oral anti-coagulant (NOAC) for whom their INR was not adequately controlled with warfarin ^{9,42,53}

c) Process indicators – drug specific with patient identity data

The opportunities to develop indicators improve dramatically with the increasing availability of encrypted patient identifiers that facilitate studies of the incidence and the prevalence of drug use ^{48,54,55}. The incidence and prevalence may then be assessed in relation to other treatment alternatives and/or the incidence or prevalence of the target disease.

Other drug-specific indicators that could be derived from patient identity data include the proportion of patients initiated on a new medicine previously treated with the first line drug, e.g.:

- Proportion (%) of patients prescribed DPP-IV inhibitors previously treated with metformin ($A/B * 100$ where A = all patients prescribed a DPP-IV inhibitor previously treated with metformin and B = all patients prescribed a DPP-IV inhibitor)
- Proportion (%) of patients prescribed new oral anticoagulants (NOACs) previously treated with warfarin ($A/B * 100$ where A = all patients prescribed a NOAC previously treated with warfarin and B = all patients prescribed a NOAC)

Proportion of patients prescribed the new medicine for concomitant treatment (good or bad), e.g.:

- Proportion of patients initiated on telaprevir for the treatment of hepatitis C in combination with peginterferon alfa and ribavirin and who have had their genotype assessed ^{5,56}

Persistence of use, e.g.:

- Proportion of patients persistent on NOACs after one year given concerns generally with persistence of medicines in patients with chronic asymptomatic conditions ⁵⁷

d) Process indicators – disease specific

These indicators assess the rational use of a new medicine in relation to a disease/diagnosis or the proportion of patients with a certain condition initiated on a drug. These can be considered nationally, regionally or locally depending on the healthcare system and its funding ^{9,42,58}. Examples include the proportion of patients with hepatitis C who achieve a sustained virologic response (SVR) with new drugs such as the bocepravir and in combination. This may also be an intermediate outcome measure. However, there have been concerns with the objectivity of this measure ^{59,60}

Such indicators could also assess the proportion of patients initiated on a new medicine who are prescribed it according to agreed recommendations and not as “off-label”, e.g. Proportion of medicines prescribed that adhere to agreed guidelines in a predefined clinic, healthcare or national setting for use, e.g. for dabigatran ^{9,42}.

e) Outcome indicators – disease specific (with patient identity data)

These indicators focus on the desired or not desired outcome of the new therapy, e.g., by using intermediate/surrogate markers:

- Proportion of patients initiated on DPP-IV inhibitors achieving agreed HbA1c levels

- Proportion of patients with advanced cancers initiated on new cancer medicines achieving a desired response using a biomarker, e.g. bortezomib for the treatment of first relapse of multiple myeloma based on a 50% reduction in serum paraprotein levels (M-protein) by the fourth cycle^{46,47}
- Proportion of patients with HIV achieving an agreed reduction in their viral load level

They may also assess more relevant outcomes on morbidity and mortality post-launch:

- % of patients achieving similar outcomes in practice versus Phase III results given potential differences in co-morbidities^{9,40-42}

However, it is important to consider when developing indicators whether there are regional, gender, socioeconomic or other differentials in the distribution of the population⁶¹ or geographical differences between countries or regions.^{58,62-64}

Development of a testing protocol

An indicator testing protocol has to apply to a multi-step and methodological process, as shown in Table 2. Such a protocol is a checklist of activities that need to be addressed in the development of quality indicators (for new innovative medicines but also in general) that will be used in implementation plans around interventions to optimize the introduction of new medicines.

Table 2: Indicator testing protocol for the managed introduction of new medicines (Source: Based on Campbell et al 2011³²)

Necessity

- Analyzing the therapeutic arena – current challenges, existing therapeutic recommendations, unmet need and the possibility for the new drug to address these needs
- Assessment of current indicators and their applicability for the new drug
- Each indicator should be underpinned by a published evidence base related to need (e.g. evidence of better efficacy, feasibility, safety or cost-effectiveness than existing drug)
- Economic modelling

Clarity

- The indicator wording is clear and precise with unambiguous language that reflects a specific domain of quality
- The indicator is within the control of the prescriber/provider that will be assessed

Content validity

- The indicator statement represents high quality care and is therefore a valid indicator of quality. There is sufficient evidence/ professional consensus to support it and there are clear benefits to the patient receiving the care (or the benefits significantly outweigh the risks).
 - Each indicator is underpinned by a published evidence base (e.g. a guideline or a well-conducted clinical trial)
 - Adherence to the indicator is based on physicians/ staff adhering to the indicator providing a higher quality of care/service than those who are not doing so.
 - Likely patient benefit

Technical feasibility and reliability of data extraction / data availability

- Ability to write and integrate data extraction specifications into health information systems from all relevant providers
- Ability to generate reproducible test reports within a reasonable time frame and budget from all relevant providers

Acceptability

- Evaluation of the testing protocol
- Alignment to patient values
- Alignment to professional values

Implementation

- Discriminate validity: assessment of indicator to discriminate between providers
- Sensitivity to change: assessment of current baseline of the indicator and potential change in baseline at the end of a piloting period
- Clinical staff are able to interpret the indicator
- Potential for *gaming/manipulation* is limited
- Changes required to implement the indicator (i.e. acquisition and/or modification of IT; changes in physical capital/staffing; changes to regulation, policies and education).
- Workload implications of implementing the indicator
- Potential barriers among different stakeholders to the implementation of the indicators
- Unintended consequences to the implementation of the indicator: positive or negative in nature (i.e. disruption to clinical or organisational workflow, 'spillovers' that may be negative (diversion of effort) or positive (encouraging general quality improvement)).

Quality measures should be subjected to a testing protocol, with indicators assessed against key attributes^{32,34}. This protocol should address the development and implementation of the indicators and the interpretation of results/ outcomes. The most essential attribute is (a) validity: the degree to which the measured value reflects the characteristic it is intended to measure, both internal validity dealing with the accuracy of data and external validity dealing with issues such as interpretability, context and representativity, i.e. when achieving the indicator target is considered better quality and when the measure is a good translation of the clinical situation¹⁵. Furthermore, indicators should be (b) relevant, (c) communicable, (d) objective (based on evidence) and (e) reliable. They should be independent of subjective judgement since it is known that self-reported data produces, for example, gross over-estimations of adherence to guidelines⁶⁵

However, the therapeutic context for the selected indicators needs to be described in order to understand the rationale behind the selected indicators. An example of such a summary is shown in Table 3 in relation to the quality of use of anticoagulants in Atrial Fibrillation.

Table 3. Therapeutic overview of Atrial Fibrillation: Rational behind the need for indicators on new oral anticoagulants (NOACs)

Quality of anticoagulants in Atrial Fibrillation (necessity, clarity and content validity)

Anticoagulation (AC) aims to reduce embolic stroke while achieving bleeding control

Quality of AC/AF therapy requires initial assessment and regular clinical check-ups:

- assessment and treatment of other risk factors for stroke, e.g., blood pressure and diabetes
- scoring the patients stroke risk using CHADS₂ or CHA₂DS₂-VASc
- treatment decision based on patient's risk-score and individual patient factors that may affect the choice of medicine and dose regimen for optimal and stable exposure over time. These factors may include renal function and drug-drug interactions as well as the patients' attitudes and compliance
- AC intensity control of warfarin PT-INR (range within 2-3), NOACs indirectly by, e.g., eGFR and clinical examination and patients reporting of nuisance bleeds *or* with direct laboratory measurements of the drug or its anticoagulation effect given appreciable variation in absorption⁴²

Potential unmet need & place in therapy of NOACs include:

- underuse of warfarin and overuse of aspirin in AF due to feasibility problems and patient attitudes
- frequent intensity checks and/or fluctuating AC intensity may be a problem in some patients
- even though NOACs may add benefit for certain patients or in certain settings where AC control is suboptimal, it should be noted that patients on NOACs also have a narrow therapeutic window and that regular controls are needed
- the limited availability of specific laboratory tests and antidotes to NOACs may cause problems in, e.g., emergency situations
- comparable cost-effectiveness between warfarin and NOAC overall, but this may vary between different health systems and settings

These relate to the attributes of necessity, clarity and content validity. The overall testing protocol (Table 2) should cover and test: (1) the necessity of new medicines, (2) data extraction from appropriate data sources to test technical feasibility and reliability, (3) cost-effectiveness modeling to assess the budget impact and (4) implementation issues associated with introducing new medicines to test their acceptability, efficacy/effectiveness, workload, any associated education and training, patient views and unintended consequences³². For example, the experience of introducing dabigatran showed increased prescriptions compared to warfarin in rural areas with less availability of warfarin monitoring clinics⁴². Examples of how the protocol can be applied to recently introduced anticoagulants (NOACs) are summarized in Table 4.

Table 4: Examples of application of new medicines to the indicator testing protocol Source: Based on Campbell et al 2011³²

Testing protocol attribute	Example 1 – proportion of patients initiated on NOAC previously dispensed warfarin	Example 2 – proportion of patients treated with NOAC with annual renal function assessment (eGFR)
<i>Type of indicator (i.e. activity, process, outcome, systems)</i>	Process indicator, drug specific requiring patient identity drug dispensing data	Process indicator, requiring access to laboratory data/medical records
<i>Necessity</i> [pre-launch]	Warfarin is a well documented drug with known safety profile and monitoring possibilities. Consequently it should be preferred for most patients	Exposure levels of NOACs increased upon decreased renal function. This may increase bleeding risk that might be avoided by dose-reduction and switching.
<i>Clarity</i> [pre-launch]	Indicators based on prescriptions issued by the physician and/or dispensed at pharmacies	Indicators based on patient follow up (measured by physicians)
Content validity [pre-launch]	Uncertain since the indicator encaptures no clinical data. Guidelines vary between countries ⁹	Stated in the Summary of Product Characteristics (SPC). Pharmacokinetic studies showing large variability in elimination due to renal function.
Technical feasibility and reliability of data extraction / data availability [pre- and peri- and post launch]	Requires patient-level pharmacy dispensing data readily available in many registries/reimbursement databases ⁴²	May be extracted manually or automatic from medical records if properly recorded
Acceptability [pre- and peri- and post launch]	Dependent on how benefit and risk of NOAC vs warfarin is communicated to and perceived by patients and physicians	Clearly relates to patient safety and should be obvious to both patients and physicians
Implementation [pre- and peri- and post launch]	Easy to use to compare practices and over time. Could be implemented with minimal workload for physicians and patients. A potential initial target may be >50%, but appropriate levels requires validation assessing clinical data. These target may change when new evidence is developed for NOACs	Easy to use to compare practices and over time. Could in most instances be implemented with minimal workload for physicians and patients. Target level should be 100% and fixed over time.

At a systems level post-launch, it is critical to collect follow-up data as well monitoring guideline/indicator adherence. In parallel, learn from the experience of the implementation of other new medicines i.e. dabigatran^{9,41,42}.

Attributes of the testing protocol for new medicines

Necessity of a new medicine

This constitutes a pre-launch activity that focuses as a prioritisation or filter stage to address the evidence base for the need of a new medicine either due to lack of efficacious drugs or safety, administration and persistence concerns. It addresses the incidence and prevalence of potential new users, the costs and effectiveness of existing medicines, the role of the new medicine in addressing multi-morbidity and economic modeling (including cost benefits; risk profile, etc.)^{9,11,12,42}. This assessment should summarise that there is sufficient evidence/professional consensus to support the use of new medicines related to quantifiable benefits to the patient receiving the care (or the benefits significantly outweigh the risks)³².

Feasibility and reliability of data sources

A common problem is that clinical data needed to develop indicators are not always easily or reliably available from routine data^{15,66}. Administrative datasets seldom contain the clinical information required to assess the value of the new medicine. Data on drug prescribing is often only available in a structured form in administrative databases, designed for other purposes than the evaluation of quality or to provide feedback. For instance drug dispensing (or reimbursement/claims) data have no embedded information on diagnoses, no laboratory data or clinical measures. Consequently, these databases can rarely be used to derive valid patient- or disease-oriented indicators. An exception is when these databases apply unique identifiers of patients with the possibility of record-linkage to other clinical information. This is the case in the Nordic countries as well as in a number of reimbursement/claims databases in Europe, North America and Asia^{48,67}.

If data are to be aggregated, it requires careful planning and analysis, which illustrates the importance of having pre-determined aims and objectives that clearly set out the reasons why the data are being collected and what they will be used for. There is a need for available data sources, which can be used to extract data as appropriate for indicators, e.g. electronic medical records, drug dispensing databases, claims databases, disease registries and patient reported data. Several recent reports show how such data can be collected^{68,69}. Multiple data sources are required and there are limitations to aggregate data, i.e. patient level data is required in all datasets that are linked. Aggregated data are data without any possibility of identifying the number of patients prescribed/dispensed the drug; except where the aggregate is the patient count itself. Typical measures in these data sets are packages, prescriptions, DDDs or expenditure⁴⁹. Patient level data includes a unique patient identifier enabling estimation of the number of patients exposed to a drug (for combination of drugs) in any time period and with longitudinal data a history of prescribing/dispensing over time.

Cost-effectiveness modeling

Cost effectiveness models assess the value of interventions against two key factors: the benefits accrued and the costs incurred, to consider whether benefits accrued by a health authority or a patient outweigh the associated costs of development or provision of the service⁷⁰. In terms of pharmaceuticals, the cost is the drug not a development or provision of service. Budget impact analysis⁷¹ or modeling provides estimates of the likely impact of a new medicine on short- and longer-term annual budgets⁷² as well as help assess the cost per Quality Adjusted Life Years (QALYs) gained⁷³ or to hypothesize a link from the new medicine with improved patient outcomes or health gains^{32,74}. This can often be linked to health gains associated with the treatment of a condition; for example, acute myocardial

infarction³². The data from such models can be used to help derive possible indicators during the pre- to peri-launch phase.

Implementation issues

Implementation issues refer to identifying issues important to consider during the actual introduction of the new medicine. This includes understanding any baseline data in terms of existing prescribing rates, which also allows sensitivity to change analyses from any baseline, understanding any changes to practice or professional routine, behavior or workload associated with the introduction of the new medicine. It also involves unintended consequences of indicators.

The key areas to address and consider before implementing indicators for new medicines are summarised in Box 1.

Box 1: Key implementation factors for the introduction of new medicines *

- Define quality and the attributes of quality to be measured
- Address how to measure each aspect of defined quality
- Decide who the customer is
- Transparent recording of conflicts of interests of all stakeholders involved
- Identify the appropriate unit of analyses (macro-meso-micro) and the availability of feasible and reliable data sources
- Data collection systems that underpin measurement before quality improvement begins (“know your baselines”)
- Multiple approaches targeting quality and safety within a systems based strategy
- A mix of structure, process and outcomes indicators
- A mix of top-down and bottom-up approaches
- Validated, field/pilot-tested indicators

NB: *Based on Campbell et al 2010¹⁰³

These include acceptability, workload, informatics and infrastructure, intended and unintended consequences as well as the views of patients, the media, politicians and the general public.

- *Acceptability*

Any new indicator should be, as far as possible, acceptable to all stakeholders affected, either in its delivery (e.g. doctors) or receipt (e.g. patients) or oversight (e.g. health managers or funders)^{11,28}. This includes alignment to professional values, policy-maker and commissioner/funder priorities and likely patient benefits. This requires in most cases pretesting of the acceptance of the indicators among the various stakeholder groups, including patients and the general public, or health professionals^{75,76}. Indeed, professional organisations are often drivers of quality improvement initiatives. This makes it essential that medical professional organisations, as well as patients, be involved in the design, use and evaluation of new medicines using indicators. For example, in Sweden, the appropriate use and monitoring of uptake of TNF-alpha inhibitor drugs have been organized by the rheumatologists and not by any payer organizations or professional medical associations⁷⁷. Similar initiatives are taken in other countries.⁷⁸⁻⁸⁰

- *Workload*

It is important to understand any workload implications of introducing new medicines or vaccines and with implementing concomitant indicators. This includes any need to undertake staff training or patient education around the new medicine if it replaces an existing prescription or any additional workload associated with a new biomarker for a new medicine^{5,9}. Additional workload will also result from the need for new data collection or data entry by patients and/or health professionals. This enables an estimation of the effort and costs associated with introducing new medicines that will also be part of any subsequent cost-effectiveness analyses.

- *Informatics and infrastructure*

Any changes required in the way in which a health system or service provider is structured or staffed in order to be able to implement the indicator should be identified pre- and peri-launch (i.e. These might include changes to computer templates or IT systems, monitoring of risk sharing arrangements, changes in physical capital or staffing and changes to practice policies or culture such as the routinely entered data into registries or electronic health records)^{9,42,68}. In terms of the introduction of new medicines, any data collected must also be tested for the technical feasibility and reliability of the data extraction³²; i.e. the capacity to generate reproducible test reports within a reasonable time frame and within budget from all healthcare providers.

- *Intended and unintended consequences*

The intended consequences of the introduction of new medicines as measured by the indicators should be determined *a priori* and may include expectation of a beneficial effect on patient outcomes compared to existing treatments, the level of adherence to guidelines and the level of overall utilisation/cost of the new agent. This emphasizes the importance of involving and understanding the views of different stakeholders, which may be contradictory; for example, in relation to introducing new drugs especially new premium priced drugs where there are opportunity cost implications. Any non-appropriate influences by stakeholder groups have to be avoided by assuring that respected pharmacotherapeutic and clinical experts are the drivers for defining appropriate indicators. Any conflicts of interests are declared according to an established policy to ensure that recommendations are based on scientific evidence.^{20,58, 81}

Exploring potential unintended consequences should be integral to any indicator testing protocol prior to roll out: The value of piloting is akin to a 'reality check'³². These may include ensuring that maximising quality or cost-effectiveness of care for populations with a new drug is not at the expense of jeopardising the therapeutic needs of the individual patient⁸² given that there is significant variety in how individual patients respond to new treatments, including genetic factors^{5,83}. Moreover, there is evidence that incentives based on specific aspects of care lead to poorer recorded care for non-incentivised aspects of care⁸⁴.

- *Patients' views and involvement*

Patient involvement in developing and using quality indicators is imperative. There is considerable variety in how patients respond to treatments, driven by differences in patient's individual characteristics, pharmacodynamic/kinetic differences and genetics^{5,83,85}. This requires a focus both on the 'technology' (i.e. tailored approach to avoid adverse drug reactions) and 'person' (i.e. genetic, medical or behavioural characteristics of patients including preferences). Data are required on patients' experiences, attitudes and outcomes in terms of being potentially prescribed a new medicine and the subsequent impact on their

health status and quality of life. It is important to use new social-media and techniques to monitor patient attitudes and use of therapies; for example, using e-based techniques ⁸⁶.

Implicit in the definition of rational use of medicines and all of the quality indicators is the importance of incorporating the patient perspective and providing means for (direct) patient input on the indicators where appropriate. Rational use requires patients to be knowledgeable about new medicines and have timely affordable access to appropriate medicines. Two key structural barriers are a lack of coordinated care due to fragmented healthcare systems ^{5,87} and high drug costs or copayments ^{88,89}. Despite the plethora of drug information available through websites (both legitimate and otherwise), patients still depend on their physicians to prescribe medicines that take into consideration not only their clinical condition but also their emotional, social and economic situations to manage drug regimens that may be quite complex especially with multiple conditions and targeted therapies ⁹⁰.

Increasingly drug development, and particularly clinical trials, include the patient's subjective assessment of his/her disease state and quality of life, which cannot be presumed from biometric or clinical tests alone ⁹¹. This requires patient-reported outcome measures (PROs or PROMs). Patients' perceptions of drug quality has significant impact on adherence, which is essential for achieving desired outcomes and avoiding adverse effects; although patient adherence to drug regimens is only about 50% ^{57,92}. The factors may be unintentional, such as complexity of the regimen or incompatibility with daily living (timing, frequency, preparation or storage). They may also be intentional, namely the lack of perceived benefit (especially for preventive therapies) and/or serious adverse effects⁹³.

The consequences of non-adherence, and in some cases even partial non-adherence, to new medicines impact not only the patient outcomes but also the health system, resulting in increased hospitalizations and deteriorating health status. The health economic impacts may be considerable, calling for the inclusion of patient adherence in calculating the pharmacoeconomics when comparing new and existing therapies ⁹⁴.

Discussion

We have shown the opportunities and challenges in developing quality indicators for new medicines or vaccines and the importance of incorporating these in to a systems framework and testing protocol to monitor the quality of the use of new medicines. To date, this has been a neglected area in indicator development.

This has to be addressed with new medicines accounting for an increasing proportion of the overall costs for medicines and healthcare generally and is an area where pharmaceutical company marketing activities are intense ^{10,46,86, 95-97}. It has been demonstrated in several studies that the quality of indicators for monitoring healthcare outcomes can lead to unintended consequences and lack many recommended parts. ^{32,98,99} Moreover, the observed influences of pharmaceutical companies on decisions about appropriate indicators suggests the need to consider the risk of conflicts of interests for the involved bodies and experts, which must be recorded clearly when developing indicators ^{20,58, 81,97,100}.

We accept more research is needed to measure how well such a framework for indicator development, and its embedded indicators, would reflect health needs, capacity, structures and differences in outcome and to what extent certain differences in case-mix may influence the results. Tables 3 and 4 provide examples of how protocols for indicator development can

be applied to recently introduced NOACs for stroke prevention in atrial fibrillation to enhance appropriate prescribing. Follow-up studies have shown that excessive bleeding and deaths can be avoided by pre- and peri-launch activities including physician education and prescribing restrictions⁴². Such indicators should be seen as screening devices and should not be over-interpreted. Indicators on their own cannot provide ‘definitive’ evidence of success or failure and should be used to raise questions, not provide answers^{11,28,32}.

However, such a testing protocol and framework is intended to encourage transparency and dialogue between stakeholders including health authorities, physicians, patients and the pharmaceutical industry. This is because the pharmaceutical industry has been the principal source of information regarding new drugs enhanced by appreciable resources currently spent on marketing activities with physicians³⁸.

We hope the suggested activities will stimulate a debate that will enhance innovation in pharmaceutical companies as well as the development of national drug strategies that find new ways of improved communication between payers and providers and between these groups and pharmaceutical companies, politicians and patient organisations. Without such dialogues, it may become increasingly difficult for European countries to continue to provide equitable and comprehensive healthcare within available budgets including funding for new innovative medicines.

While indicators for new medicines, perhaps inevitably, focus on populations of patients this should not be at the expense of a focus on quality from the perspective of the needs of the individual patient^{5,31,82}. For example, knowledge about the influence of pharmacogenomics on response and toxicity of drug therapies increases the focus on personalised medicine in the development and introduction of new medicines and their assessment pre- and post launch with indicators.

Summary

Different countries need to learn from each other to achieve a transparent, consistent and equitable, and not just efficiency-based, process for managing the introduction of new medicines. Such a framework is intended to act as a testing protocol to maximize the appropriate rational introduction of a new medicine rather than acting as a barrier to the uptake of new medicines. It is essential to ensure appropriate funding for new valued drugs. The suggested framework and indicator testing protocol will be useful in assessing the utilization of new medicines and may be adapted to specific country health care settings worldwide. There would be considerable benefits, and transparency of shared information, to all key stakeholders, including pharmaceutical companies, medical and professional organisations and patient organisations, by adherence to such a framework with the common aim of improved health outcomes for patients within finite resources. There is a need for greater collaboration between countries when looking to develop indicators, in particular when addressing orphan drugs or rare diseases⁵. International collaboration is especially important when evaluating new premium priced biological drugs to help ensure the optimal use of budgets for patients, physicians and health authorities given the appreciable number in development at envisaged high costs^{5,25-27,101,102}.

In conclusion, we hope this paper will stimulate debate about the managed introduction of new medicines and strategies for effective introduction in different countries; as well as the need for an agreed indicator testing protocol that covers pre-launch and post-launch activities

and are transparent and consider risks of conflicts of interest. The introduction of new premium priced drugs is the greatest challenge to the European ideals of continued provision of equitable and comprehensive healthcare in Europe¹⁰. A more structured approach would help optimise the managed entry of new medicines and vaccines and enhance future funding.

Competing interests

No author has a competing or financial competing interest to declare. The majority of authors are employed by health authorities, health insurance companies, physician associations or are advisers to them working in universities or for other independent organisations. All authors are active within Drug and Therapeutics committees and/or other regional, national and international groups involved in initiatives to help optimise the managed entry of new drugs. The content of the paper and the conclusions are those of each author and may not necessarily reflect those of the organization that employs them.

Authors' contributions

SC, BW, BG and LLG conceived the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final version of the manuscript.

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