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Sub-Categorising the Expected Value of Perfect implementation (EVPIM) to Identify When and Where to Invest in Implementation Initiatives

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Abstract

Purpose

Clinical practice variations and low implementation of effective and cost-effective health care technologies is a key challenge for health care systems and may lead to sub-optimal treatment and health loss for patients. The purpose of this work was to sub-categorise the expected value of perfect implementation (EVPIM) to enable estimation of the absolute and relative value of eliminating slow, low and delayed implementation.

Methods

Building on the EVPIM framework, this work defines EVPIM sub-categories to estimate the expected value of eliminating slow, low or delayed implementation. The work also shows how information on regional implementation patterns can be used to estimate the value of eliminating regional implementation variation.

The application of this sub-categorisation is illustrated by a case study of the implementation of an antiplatelet therapy for the secondary prevention after myocardial infarction in Sweden. Incremental net benefit estimates (INB) are based on published cost-effectiveness assessments and a threshold of SEK 250,000 (£22,300) per QALY.

Results

In the case study, slow, low, and delayed implementation was estimated to represent 22%, 34%, and 44% of the total population EVPIM (2,941 QALYs or SEK 735 million), respectively. The value of eliminating implementation variation across health care regions was estimated to 39% of total EVPIM (1,138 QALYs).

Conclusion
Sub-categorizing EVPIM estimates the absolute and relative value of eliminating different parts of sub-optimal implementation. By doing so, this approach could help decision makers to identify which parts of sub-optimal implementation are contributing most to total EVPIM and provide the basis for assessing the cost and benefit of implementation activities that may address these in future implementation of health care interventions.
Introduction

Health gains from effective and cost-effective health care technologies are realised only when they are implemented in clinical practice. Not implementing and utilising effective and cost-effective technologies as intended by reimbursement authorities and clinical guidelines lead to sub-optimal treatment and health loss for patients. In fact, slow implementation and clinical practice variations has been identified as a key challenge for health care systems, and considerable implementation variation exists within and across countries.\textsuperscript{1,2} Efforts, such as decision support tools, quality registries and financial incentives, are being employed to address this issue,\textsuperscript{3,4} but there is limited research regarding the costs of suboptimal implementation, and its potential to inform decision makers and researchers on how best to address the problem of low and varying implementation.

Work by Fenwick et al. (2008) outlined a framework for estimating the expected value of perfect implementation (EVPIM) that estimates the value of increasing implementation from the current or expected level of implementation up to a perfect level of implementation.\textsuperscript{5} The EVPIM represents an upper limit to the value of improving implementation, much in line with how the expected value of perfect information (EVPI) provides an upper limit for the value of further research regarding a specific decision problem.\textsuperscript{5,6}

Applications and extensions of the EVPIM framework have formalised and investigated the expected value of specific implementation strategies (EVSIM), estimating the value of specific (non-perfect) improvements in implementation that may be achieved by actual or hypothetical implementation strategies.\textsuperscript{7--17} Some of these contributions have also demonstrated how the framework can be used to estimate the value of improving implementation in specific subgroups,\textsuperscript{10,11} estimating the value of implementation improvements resulting from further evidence being generated,\textsuperscript{7,12--17} and taking into account, as well as predicting, future implementation patterns.\textsuperscript{10--15} These contributions have improved
the applicability and versatility of the EVPIM and EVSIM framework in assessing the value of implementation strategies based on retrospective as well as predicted future implementation patterns. Despite these developments, it has not yet been demonstrated how the EVPIM framework can be used to identify the potential underlying causes and hurdles for sub-optimal implementation and how EVPIM can support decision makers in addressing the challenge of sub-optimal implementation.

The purpose of this work is to outline a sub-categorization of EVPIM to identify the potential value of eliminating different parts of sub-optimal implementation, such as slow, low and delayed implementation. Along the lines of expected value of partial perfect information (EVPPI) when evaluating decision uncertainty, this sub-categorization can identify the absolute and relative value from eliminating different parts of sub-optimal implementation and thus provide decision makers with relevant information regarding where, and potentially how, to direct resources to address them. The approach is illustrated using an example from cardiovascular disease; the implementation of ticagrelor as secondary prevention after myocardial infarction (MI) in Sweden. This is followed by a general discussion of how the proposed sub-categorisation can be applied to past as well as predicted future implementation patterns to support decision makers in identifying when and where to invest in implementation activities.

Methods

The EVPIM framework set out by Fenwick et al. (2008) defines the (per patient) expected value of perfect implementation as the value of improving implementation from the current or expected level of implementation \( p \) to a perfect level of implementation. This is formalised in Equation 1, where expected
incremental net benefit (INB)\textsuperscript{ii} is defined as the expectation over some uncertain parameters \( \theta \) (\( E_{\theta \text{INB}}(\theta) \)).\textsuperscript{5,10,11}

\[
(1) \text{EVPIM} = (1 - \rho) \text{INB}
\]

Population EVPIM (\( p\text{EVPIM} \)) is the product of the per patient EVPIM and the number of eligible patients (\( I_t \)) in each time periods from when the technology becomes available (\( t_0 \)) until the technology loses relevance (\( T_t \)), given the discount rate \( r \) (Equation 2 and Figure 1.a).

\[
(2) p\text{EVPIM} = \sum_{t=0}^{T} \frac{I_t}{(1+r)^t} (1 - \rho_t) \text{INB}_t
\]

The population value of a specific implementation strategy (\( p\text{EVSIM} \)) that improves implementation to \( \rho^{IM} \) compared to the actual/expected level of implication \( \rho \) without the implementation strategy is given by:

\[
(3) p\text{EVSIM} = \sum_{t=0}^{T} \frac{I_t}{(1+r)^t} (\rho_t^{IM} - \rho_t) \text{INB}_t
\]

Sub-categorising EVPIM

In this work, we build on the previous extensions of the EVPIM framework, and propose sub-categorising EVPIM to identify the value of addressing different parts of sub-optimal implementation, with the aim of identifying where there is largest gain from improving implementation.

Slow, low and delayed implementation

Population EVPIM is sub-categorised into the expected value of eliminating slow, low or delayed implementation. As illustrated in Figure 1.b, we define the value of eliminating slow implementation

\textsuperscript{ii} INB can be defined in terms of incremental net monetary benefits (INMB) and incremental net health benefits (INHB)\textsuperscript{43,44}: INMB = \( \Delta E \ast \lambda - \Delta C \) and INHB = \( \Delta E - \frac{\Delta C}{\lambda} \); where \( \Delta E \) and \( \Delta C \) represented the incremental effect and cost, respectively, and \( \lambda \) the cost-effectiveness threshold.
(area A) as the value of increasing the implementation level from the current/expected level of implementation \( (\rho) \) to the highest level of implementation achieved/expected in any given time period \( (\text{max}(\rho)) \), in the time after implementation is started \( (t_{\text{implement}}) \). The value of eliminating low implementation (area B) is defined as the value of increasing implementation from the highest observed implementation level \( (\text{max}(\rho)) \) to an optimal level of implementation, from the time when implementation starts. The value of eliminating delayed implementation (area C) is defined as the value of achieving perfect level of implementation already from the time when the technology becomes available/approved/recommended for use, which in the case of pharmaceuticals in the EU would be the time of Marketing Authorisation Approval or when recommended by health technology assessment (HTA) authorities. The value of eliminating delayed implementation (area C) is divided into the value of eliminating implementation delay without improving the highest observed implementation level (Area C1) and the value of eliminating the implementation delay and gaining perfect level of implementation (Area C2)\(^{\text{iii}}\). Each of these sub-categories of \( pEVPIM \) represent the expected value of different specific implementation improvements, i.e. \( pEVSIM \), as further detailed in the equations outlined in Table S1 of the supplementary appendix.

[Figure 1 about here]

This sub-categorisation identifies the absolute gains of eliminating slow, low and delayed implementation, as well as what proportion of \( pEVPIM \) that is related to each of these parts of sub-optimal implementation. Combined, the \( pEVSIM \) of eliminating slow, low and delayed implementation (areas A, 

\(^{\text{iii}}\) The value of eliminating implementation delay presented here assumes that the implementation patterns would be the same and that they are simply moved back to an earlier starting point. For simplicity and ease of graphical representation, this work assumes that the value of eliminating implementation delay is captured in the period until implementation starts rather than over time, as a parallel shift in the implementation curve would entail. The undiscounted results are the same, but with a positive discount rate this would lead to a slight overestimation.
B and C), make up the pEVPIM, i.e. the value of achieving instant and full implementation, as Andronis and Barton\textsuperscript{7} described pEVPIM. In this work we use the term “perfect level of implementation” to represent “full” implementation in all eligible patients, and “perfect implementation” as instantaneous achievement of such perfect level of implementation.

**Accounting for regional implementation variation**

A further dimension to consider is implementation variation across different health care entities, i.e. health care regions, hospitals, health care clinics or similar. Implementation variation is a major challenge for health care systems and was an important driver in the development of the National Institute for Health and Care excellence (NICE), set up to overcome the so-called “post-code lottery” in England.\textsuperscript{18,19}

By incorporating implementation variation in the sub-categorisation of EVPIM we can estimate the proportion of EVPIM that is related to implementation variation.

We define the value of eliminating implementation variation (Area D) as the value of increasing implementation up to the level of the highest implementing entity ($\rho_t^{\text{high}}$) in each time period, from the start of implementation (Figure 1.c). The value of eliminating implementation variation comes from reducing slow and/or low implementation in those health care entities that have lower level of implementation than the highest implementing entity. Unless the highest implementing entity has achieved perfect implementation there will still be value in addressing additional slow and low implementation compared to the implementation in the highest implementing entity. These values are here defined as the value of eliminating additional slow implementation (Area E) and the value of eliminating additional low implementation (Area F), compared to the highest implementing entity, as outlined in Figure 1.c. The value of eliminating delayed implementation (Area C) remains the same as previously outlined, but C\textsubscript{2} is further divided into C\textsubscript{2a} representing the value of eliminating delay as well as
increasing implementation to the highest observed implementation level ($\rho_t^{high}$); and $C_{2b}$ the value of eliminating delay as well as increasing implementation to the perfect level of implementation.

This sub-categorisation shows the absolute and relative value of addressing regional implementation variation compared to eliminating slow, low or delayed implementation. There may be reasons for not benchmarking against the level of the single highest implementing entity. Instead, $\rho_t^{high}$ can be defined as the level of implementation in the top 3, top 5 or top 50% of implementing entities, as illustrated in the case study.

Case study

We illustrate the EVPIM sub-categorisation outlined above using a case study from cardiovascular disease. The case study is based on the implementation of the oral P2Y12-inhibitor ticagrelor for the secondary prevention after MI in Sweden. Ethical approval for this case study was granted from the regional ethics board in Linköping, Sweden (Regionala etikprövningsnämnden i Linköping; Dnr 2018/26-31).

Ticagrelor was approved by the EMA on December 3rd 2010 for “...prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes...” The Swedish Dental and Pharmaceutical benefits board (TLV) deemed ticagrelor to be cost-effective and granted it reimbursement on June 9th 2011 and ticagrelor was included in the national treatment guidelines by the National board of health and welfare (Socialstyrelsen) on December 21st 2011.

Data on ticagrelor effectiveness and cost-effectiveness for this case study was sourced from a published cost-effectiveness assessment of ticagrelor in a Swedish setting, which presented a long-term cost-effectiveness assessment based on the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial

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*iv* Ticagrelor has later also been approved for the use in other indications but this analysis focuses on the implementation within the first approved treatment indication in secondary prevention of MI.
For the estimation of INB in the present case study a cost-effectiveness threshold of SEK 250,000 (approximately £22,300) per quality adjusted life year (QALY) was used; a conservative figure compared to the threshold employed by TLV in the assessment of similar technologies.\textsuperscript{27} The discount rate was set at 3\% per year in accordance with TLV’s guidelines on economic evaluations.\textsuperscript{28,29}

Estimation of ticagrelor implementation levels was based on utilisation data from the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. A full description of SWEDEHEART is available elsewhere.\textsuperscript{30,31} From this nationwide registry the number of patients (age<80 years)\textsuperscript{v} treated with ticagrelor, clopidogrel, prasugrel, or no P2Y12 inhibitor was obtained per health care region (county council) as shown in Figures 2.a and 2.b.

We defined the number of eligible patients as the number of patients that received dual antiplatelet treatment, i.e. we excluded patients who received clopidogrel or ASA as monotherapy in the main analysis. Hence, the level of ticagrelor implementation is estimated as the proportion of dual antiplatelet treated patient who received ticagrelor and ASA. Based on this definition, the highest (average) level of implementation ($\max(\rho)$) was identified to be 79\% and the highest level achieved in a specific health care region ($\max(\rho^h_{\text{high}})$) was 94\%.

Prasugrel is another dual antiplatelet that was approved by the EMA and reimbursed in Sweden by TLV prior to the approval of ticagrelor. There was limited use of prasugrel in Sweden during 2010 and after the approval of ticagrelor (as seen in Figure S1 in the supplementary materials). However, to avoid

\textsuperscript{v} Focussing on patients age<80 years is consistent with Swedish and international guidelines recommending ticagrelor in this patient population\textsuperscript{26,45}
overestimating the value of improving ticagrelor implementation, the estimations were adjusted for the observed prasugrel utilisation by subtracting the number of additional patients treated under improved implementation with the number of patients treated with prasugrel (in effect assuming similar INB from ticagrelor and prasugrel treatment).

**Scenario analysis**

We also assessed the value of increasing implementation in some of the patients who did not receive dual antiplatelet treatment. The SWEDHEART data showed that the proportion of patients not receiving dual antiplatelet varied significantly between regions (from around 5% to 25%) (supplementary materials Figure S2). In this scenario analysis we estimated the value of increasing implementation up to the implementation level in the health care region with lowest proportion of non-treated patient. The value of increasing implementation in this patient population was estimated given different assumptions on INB: 1) same effect and INB as estimated from the PLATO trial; 2) double QALY gain and same cost as estimated form the PLATO trial; 3) Half the QALY gain and same cost as estimated from the PLATO trial; and 4) zero QALY gain but same cost as estimated for the PLATO trial.

We also conducted different sensitivity analysis on the threshold, treatment effect, and cost of treatment.

**Funding**

Financial support for this study was provided in part by a grant from Östergötland Region, Sweden. The funding agreement ensured the authors’ independence in designing the study, interpreting the data, writing, and publishing the results.

**Results from the case study**

The $\text{pEVPIM}$ is estimated to 2,941 QALY or SEK 735 million (£66 million) in this case study of ticagrelor implementation.
Slow, low and delayed implementation sub-categorisation

The results demonstrate that the value of eliminating slow implementation represent 22% of the $pEVPIM$, and that low and delayed implementation represent 34% and 44%, respectively (Figure 3). This indicates that the value of eliminating low implementation compared to slow implementation is around 50% higher in the case of ticagrelor implementation in Sweden.

Regional implementation variation

In terms of regional variation, it is estimated that 39% of $pEVPIM$, or 1,138 QALYs, would have been gained from eliminating regional variation. The value from further eliminating slow and low implementation is reduced compared to the previous sub-categorisation, since the majority of this value is incorporated in the value of eliminating regional implementation variation.

The sensitivity analyses demonstrated that the value of eliminating regional implementation variation was 989 QALYs and 34% of the $pEVPIM$ when estimating the value of increasing implementation up to the average implementation in the 3 highest implementing regions. This value was reduced to 647 QALYs and 22% of the $pEVPIM$ when increasing the implementation of the bottom 50% up to the average implementation level of the 50% of health care regions with highest level of implementation.

Sensitivity analysis

It was estimated that 4,575 additional patients would have been treated with dual antiplatelet if all regions had treated the same proportion of patients, as the regions with the highest proportion of dual antiplatelet treatment. The estimated value of treating these additional patients with ticagrelor varied
from -56 to 1,066 QALYs, depending on assumptions around the treatment effect and costs of treating these additional patients.

Sensitivity analyses did not show any significant impact on the results presented above for this case study. The absolute INB estimations were, as expected, impacted by different assumptions on cost, effects and threshold value; but the relationship between pEVSIM due to slow, low, delayed or varying implementation remained similar across the scenario analysis.
Discussion

Main findings from the case study

The case study of the implementation of ticagrelor demonstrates how the sub-categorisation of EVPIM can be applied to estimate the value of eliminating slow, low, delayed, or varying implementation and thus provide an upper limit for how much could have been gained from eliminating each of these parts of sub-optimal implementation. In this case study 39% of the $p_{EVPIM}$, representing 1,138 QALYs, could potentially have been gained by eliminating regional implementation variation. In fact, in the period after implementation was initiated, regional variation accounted for around 70% of the health loss due to suboptimal implementation. This demonstrates that there can be significant health gains from eliminating implementation variation, even in a relatively small country where equal access to health care is an explicit objective.\textsuperscript{32–34}

Notably, this case study is based on retrospective implementation patterns. Hence, the EVPIM and EVSIM estimates represent the loss from sub-optimal implementation rather than prospective value that can be obtained from improving implementation. Applying the proposed sub-categorisation to predictions of future implementation patterns as well as other retrospective implementation patterns would increase our general knowledge on when and where there may be greatest returns from addressing sub-optimal implementation, as discussed further below. Such general knowledge on implementation patterns may include whether regional implementation variation is a similar concern across other treatments and therapeutic areas, and if this may be used to predict future, amendable, health loss from regional implementation variation across Sweden. It should be noted that the $p_{EVSIM}$ from eliminating regional variation was 167 QALYs (representing around SEK 41.8 mil and £ 3.8 mil) in the fifth year after implementation indicating an upper limit to how much it could be worth (per year) to eliminate regional variation of ticagrelor treatment in later years.
In this case study the value of eliminating delayed implementation is estimated at 1,297, representing 44% of the pEVPIM. Around half of this value occurred in the time until TLV granted ticagrelor reimbursement (June 2011), and the remaining half in the period from the reimbursement decision until the national clinical guidelines were updated and implementation started (December 2011). We do not know if updating the guidelines earlier would have resulted in earlier implementation, but the results indicate that there may be significant gains from ensuring that treatment guidelines are updated at the same time, or as part of, the reimbursement/HTA process, similar to the NICE processes in England. It is, however, important to stress that our results do not imply that the time until HTA decision should be minimized to reduce the potential loss due to implementation delay. There are good reasons for having a rigorous HTA and cost-effectiveness assessment of new health care technologies to ensure that only those technologies that are expected to provide a positive INB are implemented, as detailed by for example Johannesen et al. (2017).35

A key challenge in all EVPIM studies, and ours is no exception, is to define the number of eligible patients. In this work we defined eligible patients as all MI patients who received dual antiplatelet therapy. In this way, the case study incorporates clinicians’ assessment of which patients that should receive dual antiplatelet treatment and potential variation in case-mix across health care regions. This estimate is conservative compared with using all MI patients indicated to receive dual antiplatelet therapy as an estimate of eligible patients. The large variation in the proportion of patients treated with dual antiplatelet therapy across regions, nevertheless, indicate that further investigation may be warranted to understand if this variation is due to different case-mix and/or varying treatment practice of MI patients across Swedish health care regions.

The benefits from improving implementation in this case study rely on a cost-effectiveness assessment based on the PLATO trial and assumes the same INB per patient treated as reported from this study. A registry study of MI patients treated with ticagrelor as secondary prevention in Sweden (N=45,073, with
11,954 patients treated with ticagrelor) found similar effectiveness of ticagrelor treatment as the PLATO trial,\textsuperscript{36} supporting the approach of this case study. Neither the PLATO trial or the study by Sahlen et al. (2016) provided evidence on significant effectiveness or cost variations for the patient population of the case study.\textsuperscript{20,23,36} This supports the assumption of constant INB per patient treated. The issue of heterogeneous INB is discussed further below.

**Strength and limitations of the proposed sub-categorisation of EVPIM**

A benefit of the proposed framework of sub-categorising EVPIM is that it identifies the value of addressing different parts of suboptimal implementation, similar to expected value of perfect parameter information (EVPPI) in the expected value of information (EVPI) framework.\textsuperscript{5,6} By disentangling the value of addressing slow, low, delayed, and varying implementation from the total EVPIM, assessment of implementation strategies addressing these different parts is facilitated. This approach also enables evaluation of the value of implementation strategies that address specific parts of sub-optimal implementation across several health care interventions or therapeutic areas, e.g. strategies that could reduce regional variation across several interventions.

The categories of slow, low and delayed implementation were selected as they represent different aspects of suboptimal implementation that potentially require different strategies to address them. Slow implementation represents the time it takes to reach the highest achieved/expected level of implementation, i.e. the loss from not getting to this level faster. In contrast, low implementation relates to the loss from the achieved/expected level of implementation being lower than the optimal level of implementation (optimal level of implementation could be defined by clinical experts, guidelines or HTA agencies). Delayed implementation represented a loss from not starting implementation earlier, which is likely linked to policy processes such as updating of treatment guidelines, inclusion on drug formularies and securing funding for new therapies. Further understanding and research into how different
implementation strategies address slow, low and delayed implementation is needed to determine the relevance of this sub-categorisation. Indeed, also to understand if there are other more relevant sub-categorisations.

When there is significant implementation variation, there is an opportunity to understand what higher implementing regions, hospitals or physicians are doing differently and aim to establish how this might be used by others. Indeed, a key reason for the development and expansion of clinical and quality registries in recent years has been to identify and understand clinical practice variations. The approach presented in this paper could help to assess the consequences of observed/expected implementation variations, estimate the value of reducing variations and help to identify patterns associated with the highest value of being improved.

The approach of sub-categorising EVPIM can be applied to retrospective implementation patterns, as in the current case study, as well as future predicted implementation patterns. Works by Grimm et al. has outlined methods for predicting future implementation patterns, based on diffusion theory and expert beliefs. Although it is not yet common practice to perform detailed predictions of future implementations patterns, this work demonstrates how EVPIM and EVSIM, as well as our proposed sub-categorisation, can be estimated prior to the introduction of new technologies.

Applications of the proposed sub-categorisations to past implementation patterns might be equally valuable for understanding how to address the issue of sub-optimal implementation. Applying this framework broadly to previously implemented technologies could identify the relative size of slow, low, delayed and varying implementation out of pEVPIM. In addition to identifying what has been the main contributor(s) of pEVPIM, this information could identify how slow, low, delayed and varying implementation differ across therapeutic areas, types of health care technologies, geographic areas, and physician speciality. Such analyses would be highly valuable in order to identify areas most in need of
implementation strategies and to indicate what type of future implementation research and strategies to investigate and employ.

A key limitation to estimating the value of eliminating slow, low, or varying implementation, as well as overall EVPIM, across healthcare technologies is the availability of implementation patterns, defining the number of eligible patients and cost-effectiveness estimates. Case studies, including ours, tend to focus on pharmaceuticals or medical devices, most likely due to the availability of published data and clearly defined patient populations. However, as exemplified by Homans and colleagues who estimated the value of guideline implementation,38–41 and Mewes et al. (2017) evaluating the value of increasing adherence to guideline-based physical exercise for cancer survivors,42 it is possible to apply the EVPIM framework to other and broader implementation assessments. Work has also shown how heterogeneous cost-effectiveness estimates may be addressed in the EVPIM framework,10,11 and the effect of non-linear costs, e.g. cases where investment in new equipment is needed, and non-linear effect, e.g. heard immunity from vaccinations, could also be accounted for in EVPIM estimations. It may be more challenging to clearly defined the time of availability for surgical procedures and changes in treatment practises compared to pharmaceuticals and medical devices, but first adoption into routine use, recommendations by clinical societies, clinical guidelines or similar could be used as alternatives for EMA or HTA recommendations.

Policy implications

Low implementation and unequal access to health care are key hurdles for health care systems around the world.1,2 Sub-categorising EVPIM could provide valuable information to policy and decision makers on how to address these issues through identifying: 1) what parts of sub-optimal implementation are contributing most to $p$EVPIM; 2) the value of eliminating different parts of sub-optimal implementation; and 3) identify regions, health care providers and therapeutic areas where there is highest value from improving implementation.
EVPIM sub-categorisation provides a way to identify and guide research and investments in implementation strategies for those parts of sub-optimal implementation that are causing the greatest loss to population health. Applying the proposed sub-categorising across health care technologies could help to assess the value of implementation strategies that address different parts of sub-optimal implementation across multiple health care technologies and therapeutic areas. In this way, EVPIM sub-categorisation could support assessment and prioritisation between implementation strategies, and help decision makers to identify what implementation strategies to fund.
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Conflicting interest

KMJ is a part-time PhD student at Linköping University and a part-time employee of Bristol Meyers Squibb AB, Sweden. The latter had no role in the present study. MH has no conflicts of interest. MJ; lecture fees from AstraZeneca and Pfizer. TJ; lecture fees from AstraZeneca, MSD and Ipsen.
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Tables

Table 1. Input to the ticagrelor case study

|                               | Ticagrelor | Clopidogrel | Δ     |
|-------------------------------|------------|-------------|-------|
| life years\textsuperscript{23} | 11.47      | 11.32       | 0.15  |
| QALY\textsuperscript{23}     | 9.66       | 9.53        | 0.13  |
| Total health care costs in SEK\textsuperscript{23} | 346,803 (£30,935) | 343,560 (£30,646) | 3,243 (£289) |
| ICER in SEK/QALY (\textcurrency/QALY)\textsuperscript{23} |            |             | 25,022 (£2,232) |
| INHB per patient in QALY*     |            |             | 0.117 |
| INMB per patient in SEK (£)*  |            |             | 29,257 (£2,610) |

*Based on a threshold of SEK 250,000 (£22,300)
Table 2. Results from the ticagrelor case study showing the INB (in QALYs) form eliminating slow (A), low (B), and delayed (C = C1+C2) implementation; as well as the value of eliminating regional implementation variation (D)

|                | 2011 | 2012 | 2013 | 2014 | 2015 | Total | % of pEVPI M |
|----------------|------|------|------|------|------|-------|--------------|
| pinB           | 6    | 550  | 813  | 892  | 908  | 3,168 |              |
| pEVPI M        | 1,297| 730  | 381  | 295  | 239  | 2,941 |              |
| The value of eliminating slow, low and delayed implementation |      |      |      |      |      |       |              |
| A              | 0    | 463  | 133  | 48   | 0    | 644   | 21.9%        |
| B              | 0    | 266  | 249  | 247  | 239  | 1,000 | 34.0%        |
| C              |      |      |      |      |      |       |              |
| C1             | 1,297| 0    | 0    | 0    | 0    | 1,297 | 44.1%        |
| C2             | 1,026| 0    | 0    | 0    | 0    | 1,026 | 34.9%        |
| The value of eliminating regional implementation variation |      |      |      |      |      |       |              |
| D              | 26   | 504  | 232  | 208  | 167  | 1,138 | 38.7%        |
| E              | 0    | 146  | 75   | 13   | 0    | 234   | 8.0%         |
| F              | 0    | 79   | 74   | 74   | 71   | 298   | 10.1%        |
| C1             | 1,026| 0    | 0    | 0    | 0    | 1,026 | 34.9%        |
| C2a            | 190  | 0    | 0    | 0    | 0    | 190   | 6.5%         |
| C2b            | 55   | 0    | 0    | 0    | 0    | 55    | 1.9%         |
| Sensitivity analysis |      |      |      |      |      |       |              |
| Increased implementation level up to: |      |      |      |      |      |       |              |
| highest implementing region (D) | 26   | 504  | 232  | 208  | 167  | 1,138 | 38.7%        |
| Top 3 regions  | 13   | 446  | 215  | 187  | 126  | 989   | 33.6%        |
| top 5 regions  | 9    | 418  | 198  | 171  | 99   | 896   | 30.5%        |
| Top 10 regions | 3    | 282  | 162  | 132  | 68   | 647   | 22.0%        |
| Different assumptions on effect from increasing proportion receiving dual antiplatelet therapy |      |      |      |      |      |       |              |
| 1) same effect and INB as estimated from the PLATO trial | 505  |      |      |      |      |       |              |
| 2) double QALY gain and same cost as estimated form the PLATO trial | 1,066|      |      |      |      |       |              |
| 3) half the QALY gain and same cost as estimated from the PLATO trial | 225  |      |      |      |      |       |              |
| 4) zero QALY gain but same cost as estimated for the PLATO trial | -56  |      |      |      |      |       |              |
Figures

Figure 1. A stylised example illustrating (a) the population expected value of perfect implementation ($p_{EVPIM}$); (b) the expected value of eliminating slow (A), low (B) and delayed ($C = C_1 + C_2$) implementation; and (c) the expected value of eliminating regional implementation variation (D).

- $p$ is the average level of implementation.
- $p_{high}$ is the level of implementation in the highest implementing region.
- $\max(p_t)$ is the highest average level of implementation.
- $\max(p_{high})$ is the highest level of implementation achieved in the highest implementing region.
- $t_0$ is the time when the technology becomes available for use.
- $t_{implement}$ is the time when implementation starts.
Figure 2. (a) Number of MI patients (age<80) with and without P2Y12 inhibitor in Sweden; and (b) Proportion of dual antoplatelet treated MI patients (age<80) receiving ticagrelor per health care region in Sweden.
Figure 3. The incremental net health benefit from (a) eliminating slow (A), low (B) and delayed (C) implementation; and (b) eliminating regional implementation variation (D), based on the ticagrelor case study.
Figure S1. Proportion of MI patients (age<80) receiving prasugrel by Swedish county councils
Figure S2. Proportion of MI patients (age<80) receiving no P2Y12 inhibitor by Swedish county councils
Figure S3. Proportion of MI patients (age<80) receiving clopidogrel by Swedish county councils
Table S1. Definitions of the value of eliminating slow, low, delayed and varying implementation

| Description | Area | Equation |
|-------------|------|----------|
| Population INB | | \( p\text{INB} = \sum_{t=0}^{T} \frac{I_t}{(1+r)^t} \rho_t \text{INB}_t \) |
| Slow, low and delayed implementation | | |
| Population EVPIM | | \( p\text{EVPIM} = \sum_{t=0}^{T} \frac{I_t}{(1+r)^t (1-\rho_t)} \text{INB}_t \) |
| Eliminating slow implementation, i.e. implement up to \( \text{max}(\rho_t) \) from the time when implementation starts (\( t_{\text{implement}} \)) | A | \( p\text{EVSIM}_A = \sum_{t=t_{\text{implement}}}^{T} \frac{I_t}{(1+r)^t (\text{max}(\rho_t) - \rho_t)} \text{INB}_t \) |
| Eliminating low implementation, i.e. implement in 100%-\( \text{max}(\rho_t) \) from \( t_{\text{implement}} \) | B | \( p\text{EVSIM}_B = \sum_{t=t_{\text{implement}}}^{T} \frac{I_t}{(1+r)^t (1- \text{max}(\rho_t))} \text{INB}_t \) |
| Eliminating implementation delay, i.e. implement from the time of availability (\( t_0 \)) rather than time \( t_{\text{implement}} \) | C | \( p\text{EVSIM}_C = \sum_{t=0}^{t_{\text{implement}}} \frac{I_t}{(1+r)^t} \text{INB}_t \) |
| Eliminating implementation delay given actual/expected implementation pattern | C1 | \( p\text{EVSIM}_{C1} = \sum_{t=0}^{t_{\text{implement}}} \frac{I_t}{(1+r)^t} \text{max}(\rho_t) \text{INB}_t \) |
| Eliminating implementation delay in 100%-\( \text{max}(\rho_t) \) | C2 | \( p\text{EVSIM}_{C2} = \sum_{t=0}^{t_{\text{implement}}} \frac{I_t}{(1+r)^t (1- \text{max}(\rho_t))} \text{INB}_t \) |
| Accounting for regional implementation variation | | |
| Eliminating regional variation in implementation, i.e. implement in \( \rho_t^{\text{high}} - \rho_t \) from \( t_{\text{implement}} \) | D | \( p\text{EVSIM}_D = \sum_{t=t_{\text{implement}}}^{T} \frac{I_t}{(1+r)^t} (\rho_t^{\text{high}} - \rho_t) \text{INB}_t \) |
| Eliminating slow implementation compared to implementation in highest implementing region, i.e. implement in \( \text{max}(\rho_t^{\text{high}}) - \rho_t^{\text{high}} \) from \( t_{\text{implement}} \) | E | \( p\text{EVSIM}_E = \sum_{t=t_{\text{implement}}}^{T} \frac{I_t}{(1+r)^t} (\text{max}(\rho_t^{\text{high}}) - \rho_t^{\text{high}}) \text{INB}_t \) |
Eliminating low implementation compared to highest observed implementation level, i.e. implemented in 100%-max($\rho_t^\text{high}$) from t$_{\text{implement}}$

| Term | Formula |
|------|---------|
| pEVSIM$_F$ | $pEVSIM_F = \sum_{t=t_{\text{implement}}}^T \frac{I_t}{(1+r)^t} (1 - max(p_t^\text{high}))INB_t$ |

Eliminating implementation delay given implementation pattern in the highest implementing region

| Term | Formula |
|------|---------|
| pEVSIM$_{C_{2a}}$ | $pEVSIM_{C_{2a}} = \sum_{t=0}^{t_{\text{implement}}} \frac{I_t}{(1+r)^t} (max(p_t^\text{high}) - max(p_t))INB_t$ |

Eliminating implementation delay in 100%-max($\rho_t^\text{high}$)

| Term | Formula |
|------|---------|
| pEVSIM$_{C_{2b}}$ | $pEVSIM_{C_{2b}} = \sum_{t=0}^{t_{\text{implement}}} \frac{I_t}{(1+r)^t} (1 - max(p_t^\text{high}))INB_t$ |

INB$_t$ is the expected incremental net benefit defined as the expectation over some uncertain parameters $\theta$ (E$_\theta$INB($\theta$)) at time $t$, which can be estimated in terms of incremental net health benefit (INHB) or incremental net monetary benefit (INMB): INHB = $\Delta E - \Delta C/\lambda$; INMB = $\Delta E \times \lambda - \Delta C$, where $\Delta E$ and $\Delta C$ is the incremental effect and cost, respectively, and $\lambda$ is the cost-effectiveness threshold

$I_t$ total number of eligible patients in time period $t$

$r$ is the discount rate

$\rho_t$ is the actual/expected level of implementation in time period $t$

$max(\rho_t)$ is the highest (average) level of implementation observed across all time periods

$\rho_t^\text{high}$ is the implementation level in the highest implementing region at time $t$

$max(\rho_t^\text{high})$ is the highest level of implementation observed in any region across all time periods

$T$ is the time at which the intervention loses relevance

$t_0$ is the time when the technology becomes available for use

$t_{\text{implement}}$ is the time at which implementation starts
