

FINAL REPORT

# **Social Impact of innovative medicines – a systematic approach to capture the societal and macroeconomic dimension of medicines**

**A Meta Study for Novartis**

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## **Acknowledgement**

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# 1 Introduction and Motivation

With an ever-increasing amount of investment in medical research and development (R&D) by national agencies and pharmaceutical companies, breakthrough innovations are expected to transform care and treatment of patients. The global spending in pharmaceutical research grew at an annual rate of about 4 percent between 2010 and 2018 and is expected to grow at a rate of 3 percent in the coming years<sup>1</sup>. Such developments are resulting in important advances and discoveries that are likely to result in improved population health<sup>2,3</sup>. For example, the development of personalized medicines is enabling physicians to tailor treatments to individual needs, and immunotherapies are harnessing the patient's own immune system to fight diseases such as cancer<sup>4</sup>.

Innovative medicines not only provide direct health benefits to the patients (e.g. reduced mortality, or increased quality of life), but also drive productivity gains in both the economy and society. Medicines are considered one of the six health system building blocks and are interconnected with other components of a health system<sup>5</sup>. New medicines and other health technologies have revolutionized medical practice and these advances have contributed to economic and social gains, by building healthier and thus more productive societies<sup>6,7</sup>. Improved health triggers economic growth through various channels, such as improving labor productivity, savings or investments in education and other forms of human capital<sup>8-10</sup>. Measurement of the burden of disease provides decision-makers with much-needed information on the extent to which a specific disease disrupts or reduces economic production and/or consumption<sup>11</sup>. This information, combined with evidence on how health technologies may contribute to alleviate these adverse impacts, provides a vital argument in the justification for greater health investments. However, evidence in this regard is scarce. Additionally, from a health system perspective, it is important to understand how interventions in the pharmaceutical sector affect the rest of the health system.

Furthermore, there is a perception of inappropriate market behavior by pharmaceutical companies, leading to excessive pricing as well as access and availability issues<sup>12,13</sup>. That said, such perceptions also fail to acknowledge the value medicines bring (beyond clinical benefits) for patients and societies. Against this background, the concept of value beyond clinical benefits has increasingly gained momentum in recent years. Healthcare systems are urged to pay for drugs in relation to the value they bring to patients and society. There is, however, no generally accepted definition of value in this context<sup>13</sup>. Hence, there is a need to shed light on not only the therapeutic benefits that medical innovations deliver but also on their contributions towards economic activities and general prosperity.

In the absence of a consensus on the definition of "value" of a medical innovation, we express the value of medical innovation as the monetized time gained for activities that contribute to social welfare. WifOR applies a methodology through which the value of a medical innovation is estimated from a broader macroeconomic perspective that is not limited to its clinical benefits but also accounts for its effects on the economy and the society<sup>14-16</sup>. This provides helpful insights into value creation through investments in medical R&D which are of interest for various stakeholders, including payors and investors.

This paper describes and discusses the "Social Impact" methodology developed by WifOR to comprehensively estimate the social and economic value of medical innovations that goes beyond health benefits. In the next section, the paper provides a brief overview of the various analytical methods adopted by the health technology assessment (HTA) agencies. Next, the paper discusses the Social Impact of medicines approach in general and illustrates a case study. Finally, the paper discusses the assumptions, limitations used in Social Impact approach and the implications thereof. We also describe how the Social Impact approach complements the current methodologies used in health economic evaluations.



# 2 Current analytical methods used in HTAs

In many health care systems, value assessments for new medicines take place within the framework of a formal health technology assessment (HTA). HTA is a systematic evaluation of the properties and effects of a health technology, addressing the direct and intended benefits of this technology, as well as its indirect and unintended consequences, and aims mainly at informing decision-making regarding regulatory approval, access, and reimbursement of health technologies. When assessing the effectiveness of health technologies or interventions, HTAs assess effectiveness of health technologies in terms of producing health gains, measured in clinical units. An approach is to convert clinical outcomes into gained life years, adjusted for their quality, known as quality-adjusted life years (QALYs), and apply a cost<sup>i</sup> per QALY gained<sup>17-19</sup>. This is known as cost-utility analysis (CUA).

While QALY is a well-established metric, there are challenges to this approach when using a societal perspective to valuing health. As a result, it has been the subject of debate for several years. QALYs do not capture all relevant dimensions of value. Among these are benefits that accrue not only to patients but also to caregivers, employers, or society at large<sup>20</sup>. Reed et al. (2019) also question if value elements such as the hope associated with the possibility of a cure or the value of preservation of fertility in cancer treatment, for example, are adequately captured by QALYs<sup>21</sup>. Further, evidence shows that aspects such as severity of illness or other patient characteristics are also relevant to how individuals and societies assign value to health gains, however these are not captured in QALYs<sup>17,22</sup>.

To counter some of these concerns, several HTA bodies are adopting a wider perspective to the evaluation of medicines and have shown interest in elements beyond QALYs. Disability-adjusted-life years (DALYs) are, for example, an alternative health index used in cost-effectiveness analyses. The DALY measures the number of healthy years lost by relating the reduction in life expectancy to the years lost due to disability. The DALY provides an estimate of the burden of disease, such as infectious diseases, which is useful in global health priority setting<sup>23</sup>. The WHO uses DALYs in its Global Burden of Disease Study<sup>24</sup>.

The Dutch and Swedish reimbursement guidelines, as well as those of the provincial HTA payer in Quebec, Canada, specifically call for the inclusion of costs related to productivity<sup>25</sup>. When a broader societal perspective is of interest to the decision-maker, countries including Australia and Canada suggest adopting a wider perspective, allowing productivity costs to be included if productivity is likely to be substantially affected by a new health technology<sup>26,27</sup>. When assigning a value to QALYs gained, the UK National Institute for Health and Care Excellence (NICE) takes into account end of life situations<sup>28</sup>. Swedish guidelines also adjust the cost per QALY threshold to account for “need” that is related to the disease severity<sup>29</sup>.

Nevertheless, in most cases, the use of broader value elements remains implicit and unsystematic<sup>25</sup>. In recent years, various health care associations, researchers and decision-makers have called for establishing broader value frameworks that consider a variety of value elements. These range from frequently mentioned but inconsistently used elements such as patients' productivity to novel and more strongly debated elements e.g. scientific spillovers. Several institutions and research organizations have developed value frameworks to assess the value of drugs, including the HTA Core Model (European Network for Health Technology Assessment)<sup>30</sup>, American Society of Clinical Oncology (ASCO) Net Health Benefit (NHB) Assessment Tool<sup>31</sup>, the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale<sup>32</sup>, the National Comprehensive

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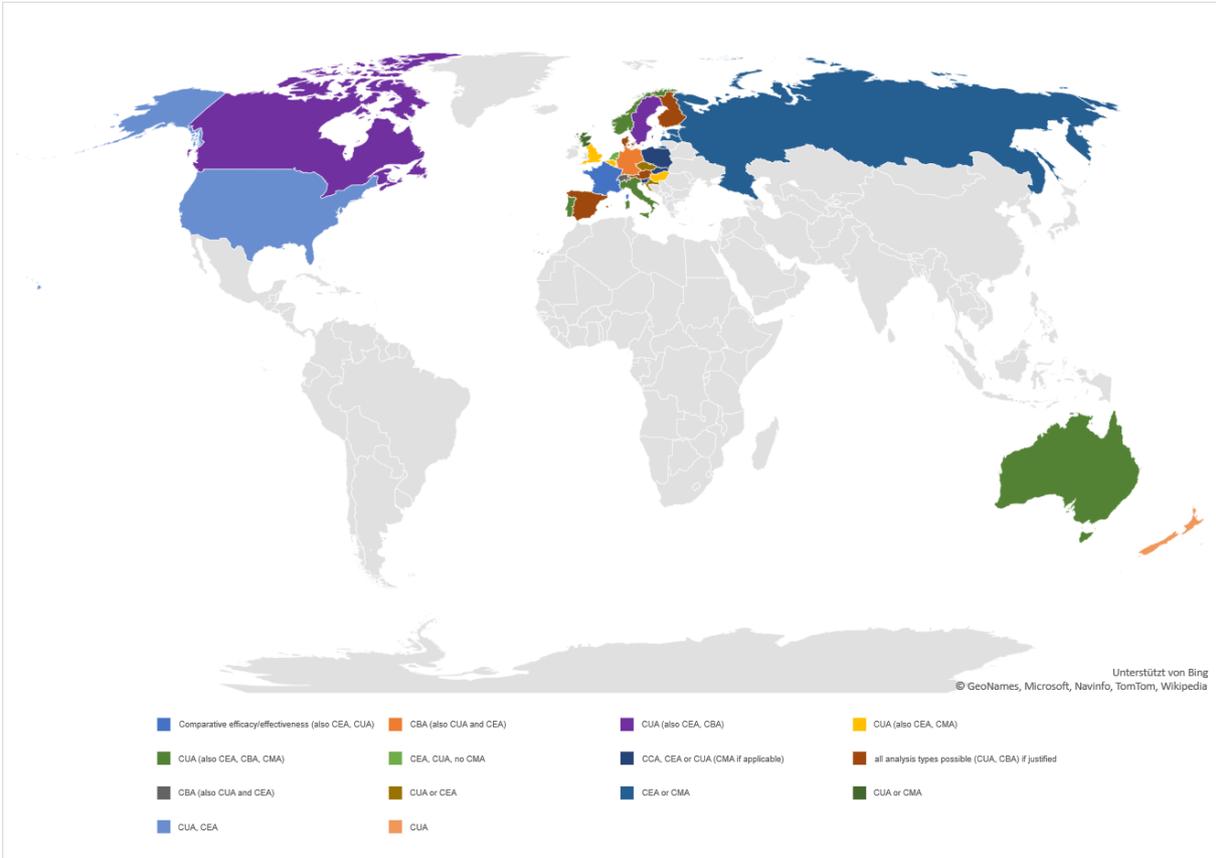
<sup>i</sup> Cost associated with use of drug relative to a standard of care. Costs generally include administration, adverse events, clinician visits and inpatient hospitalizations.



Cancer Network (NCCN) Evidence Blocks<sup>33</sup>, the Institute for Clinical and Economic Review (ICER) Value Assessment Framework<sup>34</sup>, and ISPOR Value Assessment Framework<sup>35</sup>. For more detailed information see Misra et al. (2020) which is currently under publication<sup>36</sup>.

ISPOR, as an example, suggests other methods in health evaluations, including cost- effectiveness analysis (CEA), and cost-benefit analysis (CBA). In CEA, the clinical effectiveness of two health technologies is compared, while in the less frequently used CBA, the benefits of an intervention are compared against the willingness to pay for such intervention. Although the choice of such analytical methods varies by HTA bodies, CUA and CEA are the most frequently used methods across countries (Figure 1).

Figure 1: Preferred analysis around the globe<sup>37,38</sup>



The map underlines that the preferred analytical methods are globally very heterogenous. In the US, the cost-utility analysis (CUA) and the cost-effectiveness analysis (CEA) are predominant.<sup>ii</sup> In Canada, the CUA is used along with CEA and CBA. In most of Europe (Sweden, England, Italy, Norway, Belgium, Hungary & Portugal), the CUA is the most preferred analysis, while Switzerland prefers the cost benefit analysis. In Germany and France decisions are based upon an added clinical benefit assessment.

However, there is no consensus on the most appropriate methods, and all have certain strength and limitations. Recent work has proposed different value elements to be considered in HTAs<sup>39,40</sup>, methods to appropriately capture these value elements<sup>41,42</sup> and empirical work on value elements, for example value of hope<sup>43</sup>. Finally, a wider perspective is critical to value-based pricing<sup>iii</sup> as additional information helps payers making investment

<sup>ii</sup> In contrast to many developed countries, the U.S. does not have a national HTA program to broadly evaluate health technologies and guide coverage and pricing decisions. The lack of a single national HTA organization or process reflects the current U.S. political landscape - including preference for market-oriented solutions - as well as the decentralized insurance system, under which each private and public payer makes its own coverage decisions and conducts its own price negotiations. While U.S. payers frequently use internal processes that incorporate elements of HTA to inform their coverage decisions, these processes lack transparency and involve duplicated efforts across organizations

<sup>iii</sup> Although the concept of value-based pricing has increasingly found its way into the pharmaceutical pricing and reimbursement policies, the focus of this paper is not value-based pricing but to discuss the additional value elements. Nevertheless, these additional value elements could provide good information on the price and performance of specific health technologies.



decisions to align prices of medicine and other health care services with the value achieved for patients and society.

Table 1 illustrates the different value elements considered (although some are not required or not applicable to the disease) by various HTA agencies around Europe. Furthermore, the table illustrates schematically the additional information of the macroeconomic Social Impact methodology versus existing approaches.

Table 1: Differing methodical supplements for the evaluation of medicines<sup>37,44,45</sup>

	ENG	SCT	NOR	SWE	FRA	NLD	BEL	AUT	DEU	FIN	ESP	HUN
Patient co-payments			X			X	X				X	
Early retirement			X			X						
Inability to work			X			X						
Family caregiving	X		X			X		X				
Care	X	X	X	X	X	X	X	X			X	X
Rehabilitation	X		X	X	X	X	X	X				
Medical aids, remedies & devices	X		X	X	X	X	X	X				
Out-patient treatment	X	X	X	X	X	X	X	X		X	X	X
In-patient treatment	X	X	X	X	X	X	X	X		X	X	X
Application	X	X	X	X	X	X	X	X	X	X	X	X
Pharmaceuticals	X	X	X	X	X	X	X	X	X	X	X	X
<b>Socioeconomic impacts due to better health</b>												
Productivity effects	Macroeconomic Social Impact is not considered yet											
Household production												
Voluntary work												
Spillover effects												

A high number of value frameworks aiming to facilitate decision-making based on a broader set of value elements shows that there is an acknowledgement of the limitations of the elements currently used in value assessments and accentuates the need for considering broader elements when assessing the value of medicines. Most value frameworks list productivity, in both patients and caregivers, as one or even the most relevant value element. Furthermore, most agree on the importance of fairness or equity concerns, although these are not value elements on top of health but rather aspects that need to be considered when determining the relative value of different treatments. However, value elements related to productivity are still often excluded or not considered in a systematic way. Decision-makers often exclude these outcomes, either by choosing to conduct the analyses from a third-party payer perspective or because of concerns about existing productivity costs can be measured appropriately or due to a lack of consensus about existing methods to value productivity.

This especially seems to be the case for unpaid work. However, ignoring paid and unpaid productivity costs from economic evaluations will lead to an underestimation of the true socioeconomic benefits associated with a treatment or an intervention. As a result, it gives only a partial picture of the economic implications of a treatment strategy. Furthermore, stakeholder and societal values are not adequately and systematically captured in value assessments. This leads to a lack of generalizability of assessments and limits their significance. The evidence base for decision makers is therefore incomplete, which might lead to inefficient allocation of resources.

Given the fact that diverging viewpoints on costs in economic evaluations continue to exist, and that current methodologies measure the health-related productivity costs in various ways<sup>7,46</sup>, and that unpaid work in economic evaluations has received little scientific attention, this paper aims to add to existing methodologies, improve validity and consistency, and increase awareness of the importance of including outcomes beyond health, specifically unpaid labor in health economic evaluations.

In the following, we describe the Social Impact approach using Aimovig® as an example. We also show how the Social Impact methodology is connected to and enriches the existing health economic evaluations by adding a macroeconomic perspective to value assessment of medicines. We further describe a common approach that could be applied in many settings and countries.



# 3 Taking the societal and macroeconomic perspective into account – the Social Impact approach

To what extent is a society affected by productivity losses arising from an unhealthy population? How is GDP impacted due to an unhealthy population? Most of the literature emphasizes the benefits of good health on productivity. The productivity losses at the individual or firm level (micro level) have been previously documented<sup>47-51</sup>. In economic evaluations, the question is by how much medical innovations counter such productivity losses. For several illnesses, costs due to productivity losses are higher than the direct medical costs. From societal perspective and according to the World Health Organization (WHO), an unhealthy population unable to work will reinforce labor shortages and affect fiscal budgets<sup>52</sup>. In literature, there is an on-going debate on how to value and measure health- related productivity losses.

Productivity loss due to poor health is either valued using the human capital (HC) approach<sup>53</sup> or the friction cost (FC) approach<sup>54</sup>. Both methods can produce widely different results, but both use wages or salaries as a proxy for marginal productivity<sup>55</sup>. Economic theory formalizes that a worker's wage is equivalent to his or her marginal productivity. However, labor productivity and wages often diverge in practice, due to a range of institutional and market forces. Imperfect labor markets, allowances for sick leave and underlying risk aversion often lead workers to accept wages lower than their marginal productivity<sup>49,56</sup>. Furthermore, wages and productivity diverge due to teamwork and unavailability of substitutes, as well as time- sensitivity of the output<sup>57</sup>. Therefore, there are measurement issues regarding market wages as they do not necessarily reflect the true productivity of a worker<sup>58-60</sup>.

Given these existing issues regarding the appropriate methods of measuring productivity losses, we introduce and describe a novel approach of measuring health-related productivity losses for both paid and unpaid work, using measurements such as gross value added (GVA) per employed person or gross domestic product (GDP) per capita. GVA per employed person is a useful measure that shows the contribution of each individual producer to the economy and reflects the true productivity of labor<sup>56</sup>. GVA measures the production value of goods and services minus the value of intermediate goods and services used. It is used in the estimation of GDP.<sup>iv</sup> GDP is a global welfare indicator. It measures value added by "paid" work. Other than that healthy unemployment individuals also contribute to a nation's wealth through household or other voluntary work. This value added "beyond" typical GDP is considered in the calculations and is referred as "unpaid" work.

In addition to direct productivity effects (known as indirect costs in health economic evaluations), we also consider interdependencies within the economy triggered by initial productivity effects. Building on macroeconomic input-output analysis, a change in production in one sector is expected to trigger a change in production of intermediate goods and services as well as incomes in other industry sectors, creating indirect and induced GVA effects (spill- over effects)<sup>61</sup>.

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<sup>iv</sup> GVA can be broken down by industry and institutional sector. The sum of GVA over all industries or sectors plus taxes on products minus subsidies on products gives gross domestic product.



The Social Impact approach takes a broad perspective to estimate the potential value a new medicine brings to society beyond the pure clinical scope. It enriches existing HTAs by offering a holistic societal and macroeconomic perspective. We thereby propose a common approach that could be applied to various settings, countries, and disease areas.

## 3.1 Social Impact approach – overview

Similar to the inclusion of productivity impacts in health economic evaluations, the Social Impact approach monetizes gained productive time in the terms of the human capital approach<sup>54</sup> or the friction cost approach. The Social Impact is expressed in monetary terms of avoided productivity losses that would have occurred in absence of this medicine.

We associate health gains associated with the drug of interest and translate these into outcomes such as productive time and economic impacts. The quantification of health gains is based on results from existing clinical trials, cost-utility, or cost-effectiveness studies. The appropriate measure of health outcomes varies across diseases and indications but typically includes mortality, morbidity, hospitalization, or other disease specific outcomes. These outcomes are modeled and compared between a standard of care and intervention scenario. Each health outcome is matched to corresponding medical costs and time losses for paid and unpaid work activities. The results on an individual level are the basis to extrapolate the evidence on a macroeconomic level. We are using health benefits and epidemiological data as input factors for a dynamic population model. The population simulation, in combination with macroeconomic input-output data and national accounting statistics, allows us to extrapolate individual health benefits to the population and macroeconomic level. The following section describes the Social Impact approach in detail using the case study of Aimovig® as an example. The chapter is based on a manuscript written by the authors affiliation (Seddik et al.)<sup>62</sup>.

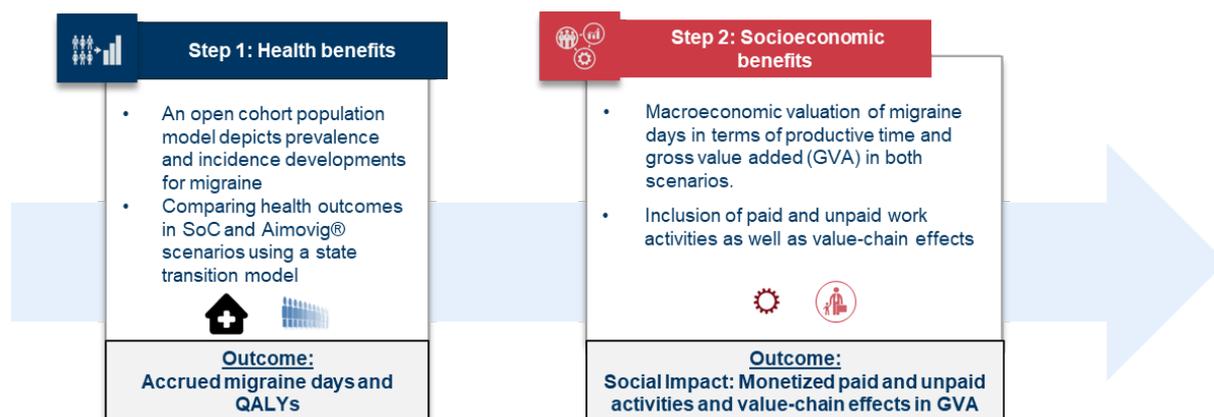
## 3.2 Social Impact of medicines – a case study:

### Aimovig®

To assess the Social Impact of Aimovig® (erenumab), we modeled two treatment scenarios: a baseline scenario (Scenario I) reflecting the situation before the launch of the first calcitonin gene-related peptide (CGRP) inhibitors, and an intervention scenario in which the patient population of interest receives Aimovig® (Scenario II). We quantified the health burden of both scenarios in terms of accumulated monthly migraine days (MMDs) and QALYs. The difference in MMDs and QALYs between both scenarios, i.e., the health gains due to the intervention, together with the associated health benefits, were therefore attributed to Aimovig® prophylaxis. Those health gains were hence valued, using a macroeconomic approach described in detail in section 3.2.2, and further reported as the Social Impact of Aimovig®. The two major steps within a Social Impact analysis are illustrated in Figure 2.



Figure 2: Overview of steps towards calculating the Social Impact of Aimovig®



### 3.2.1 Step 1: Modeling the health benefits

The health benefits are measured by conducting a state-transition model and a dynamic population model.

To quantify the health outcomes of both scenarios in terms of accrued MMDs and QALYs, a **state-transition model** was developed. The model accommodated seven health states representing the migraine severity in terms MMDs and QALYs. The following categories were defined for the model: 0, 1-3, 4-7, 8-14, 15-19, 20-23 and 24+ MMDs. The baseline distribution of the patients with over four MMDs was derived from the German Headache Consortium (GHC) Study. The GHC is a non-interventional longitudinal study conducted in Germany<sup>63</sup>.

Twelve average migraine patients (representing corresponding age and gender group) were modeled to reflect the probability of residing in one or the other health state. Furthermore, background mortality was included to account for death as a further state of the model, i.e. the state-transition model was age and gender specific.

Following the clinical data, 42% respond to the treatment (at least 50% reduction in MMDs). Those patients who do not respond to the treatment discontinue treatment after the first cycle. Furthermore, in each cycle, 2.4% discontinue treatment for any reason. Those transit back to the SoC distribution over one year. Both response and discontinuation rates are derived from the erenumab clinical trials.

For the proportion of Aimovig® patients responding to treatment in Scenario II, the average response during the first three months of prophylaxis initiation was modeled using a transition matrix derived from four clinical trials that assessed the effectiveness of Aimovig® in reducing MMDs compared to placebo. Those four studies are described in detail elsewhere<sup>64-68</sup>. Response rates were defined as 50% (or higher) MMD reduction from baseline. The post-response distribution in the health states was assumed to remain constant and was hence extrapolated over the remaining time horizon of the analysis using an identity matrix. A constant rate of 2.4% for discontinuation rate per cycle was applied. Patients discontinuing treatment were assumed to gradually transit from the responder distribution to the baseline distribution over a period of one year. Non-responders were assumed to maintain in their baseline health states. This was also assumed for the standard of care scenario (Scenario I).

To simulate the health effects amongst the entire patient population eligible for Aimovig®, a **dynamic population model** that depicts prevalence and incidence developments in the German migraine population and simulates the health outcomes was built. By doing so, we extrapolated the individual level simulation on the prevalent patient cohorts between 2020 and 2028. To derive the relative sizes of patient cohorts starting Aimovig® treatment, we used epidemiological estimates from the GBD Results Tool<sup>69</sup> together with demographic estimates<sup>70</sup> and GHC data<sup>63</sup> indicating that 40% of the overall migraine population suffers four or more MMDs. The age and gender stratified demographical data were multiplied by the corresponding prevalence and incidence rates as well as the proportion of migraine patients suffering at least four MMDs. For example, at baseline, 4.98 million males between 20 and 29 lived in Germany. 22.95% of those were migraineurs and 41% of the migraineurs suffered at



least four MMDs. By multiplying the three previous figures together, the prevalent population in this age and gender cohort was calculated to be 470 thousand patients. In this way, we derived the sizes of 12 age and gender specific cohorts for one baseline population (we refer to as the prevalence population), and similar estimates for 34 cohorts<sup>v</sup> newly starting Aimovig® treatment at each model cycle.

The average number of resulting MMDs per scenario, cohort, health state and cycle were accrued by multiplying the prevalence of the given cohort by the average number of migraine days in the given health state. The difference in the aggregate sum of MMDs for each of the two scenarios constitutes the net health benefit attributable to Aimovig® prophylaxis. Information on avoided MMDs with regards to age, gender, health state and time were reserved for the subsequent valuation steps.

## 3.2.2 Step 2: The socioeconomic valuation of migraine days

MMDs were translated to productive time loss which in turn was monetized using the human capital approach<sup>71</sup>. Lost productive time, welfare (GVA) effects, healthcare costs and QALYs were calculated and accrued for both modelling scenarios. The sequence of valuing the MMDs is described in detail below.

### Estimating the loss in productive time

Productivity effects were calculated by transforming MMDs into time lost in paid and unpaid work. The association between MMD frequency and days of absenteeism and presenteeism (for paid and unpaid work separately) were estimated using a Quasi-Poisson generalized linear model. To do so, patient responses to the Migraine Disability Assessment (MIDAS) questionnaire collected in the Aimovig® clinical trials were used. Based on the predictions of the regression model, estimates on time loss due to absenteeism and presenteeism by MMD health state were derived.

By combining the time lost due to absenteeism and presenteeism with German employment rates<sup>72</sup>, estimates from the German national accounts on industry distribution and working hours<sup>73</sup> and the German micro census<sup>74</sup>, we estimated the work time (in hours) lost in paid employment using the following formula:

$$H_{aghj}^P = \sum_{t=1}^{34} \alpha_{agh} \times \beta_{ag} \times \gamma_{agj} \times \delta_j \times \varepsilon_{ag} [Ab_h^P + Pr_h^P]$$

(1)

where

$H_{aghj}^P$  are the age, gender, health state and industry sector specific hours of paid work lost throughout the 34 cycles of the model, and the definitions of the formula's parameters and subscripts are as below:

#### Parameters

- α Aggregated migraine days
- β Employment rate
- γ Industry weight (proportion of employees)
- δ Average number of daily working hours
- ε Age and gender working hour multiplier
- AbP MMD-related absenteeism from paid work (%)

<sup>v</sup> The 8-year time horizon of the model is divided into 34 (plus 1 baseline) 84-day cycles.



PrP MMD-related presenteeism from paid work (%)

*Subscripts*

- a Age
- g Gender
- h Health state
- j Industry sector
- t Time (model cycle)

Data from the latest available German time-use survey<sup>75</sup> were used to estimate the work time loss (in hours) for unpaid work activities. The following 11 activities for unpaid work were considered: (1) gardening, (2) improvements and home repair, (3) preparation of meals, (4) maintenance of dwelling, (5) manufacturing and care of textile fabrics, (6) planning and organization, (7) purchases and procurement, (8) informal care, (9) childcare, (10) other care and (11) voluntary work. According to the market replacement cost approach<sup>76</sup>, these activities were assigned to their nearest industry equivalent<sup>77</sup>. The following formula gives the time loss for unpaid work activities:

$$H^U_{aghj} = \sum_{t=1}^{34} \alpha_{agh} \times \theta_{agj} [Ab^U + Pr^U]$$

(2)

where

$H^U_{aghj}$  is the age, gender, health state and industry sector specific number of hours of unpaid work lost throughout the 34 cycles of the model, and the definitions of the formula's parameters and subscripts are as below:

*Parameters*

- $\alpha$  Aggregated migraine days
- $\theta$  Daily hours spent on unpaid work activities
- AbU MMD-related absenteeism from unpaid work (%)
- PrU MMD-related presenteeism from unpaid work (%)

*Subscripts*

- a Age
- g Gender
- h Health state
- j Industry sector
- t Time (model cycle)



### Monetary valuation of paid and unpaid hours lost

To monetize MMDs, industry specific gross value added (GVA) per paid working hour<sup>78</sup> was multiplied by the industry specific lost working hours in paid work. Time losses in unpaid work activities were assigned to the nearest industry sector equivalent and thus the same monetization method was applied. The pairing of unpaid work activities to industry sectors is shown in Table 2.

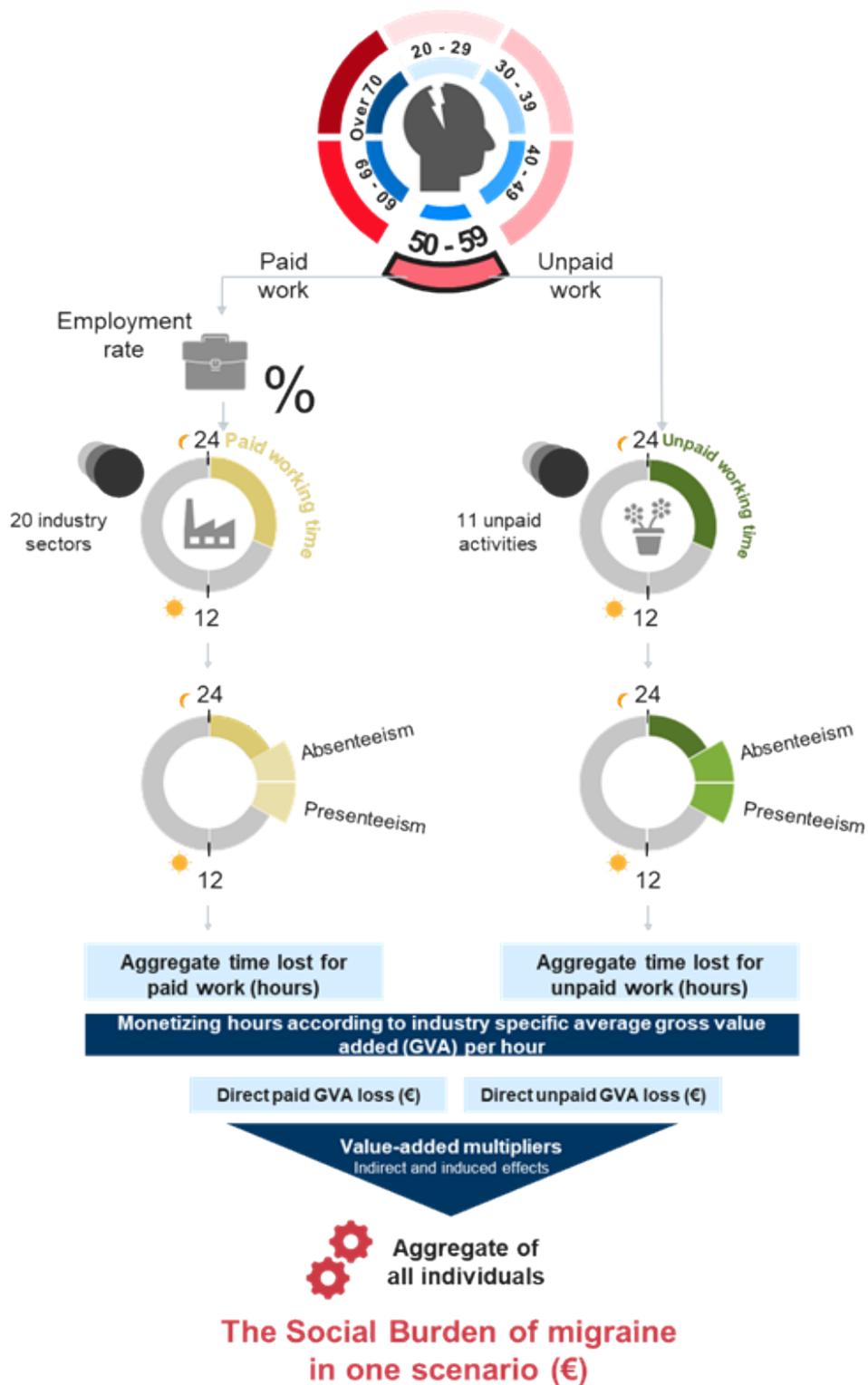
Unpaid work activities	Industry	Paid work activities
Gardening work, plant- and animal care	A	Agriculture, forestry and fishing
Constructing and craft activities	F	Construction
Preparation of meals	I	Accommodation and food service activities
Maintenance and cleaning of apartment	N	Administrative and support activities
Maintenance and cleaning of apartment (textiles)	N	Administrative and support activities
Planning and organization	N	Administrative and support activities
Shopping and services	N	Administrative and support activities
Informal help	N	Administrative and support activities
Childcare	P	Education
Other services	P	Education
Voluntary work	P	Education

Table 2: Pairing of unpaid work activities to industry sectors

In this way, we assumed that the unpaid work activities contribute the same value for individual and public wellbeing as their corresponding market equivalents. The monetization approach of MMDs is summarized in Figure 3 below.

Figure 3: Monetary valuation of a headache day

## Monetary valuation of headache days for each scenario (12 subgroups representing different gender and age groups)



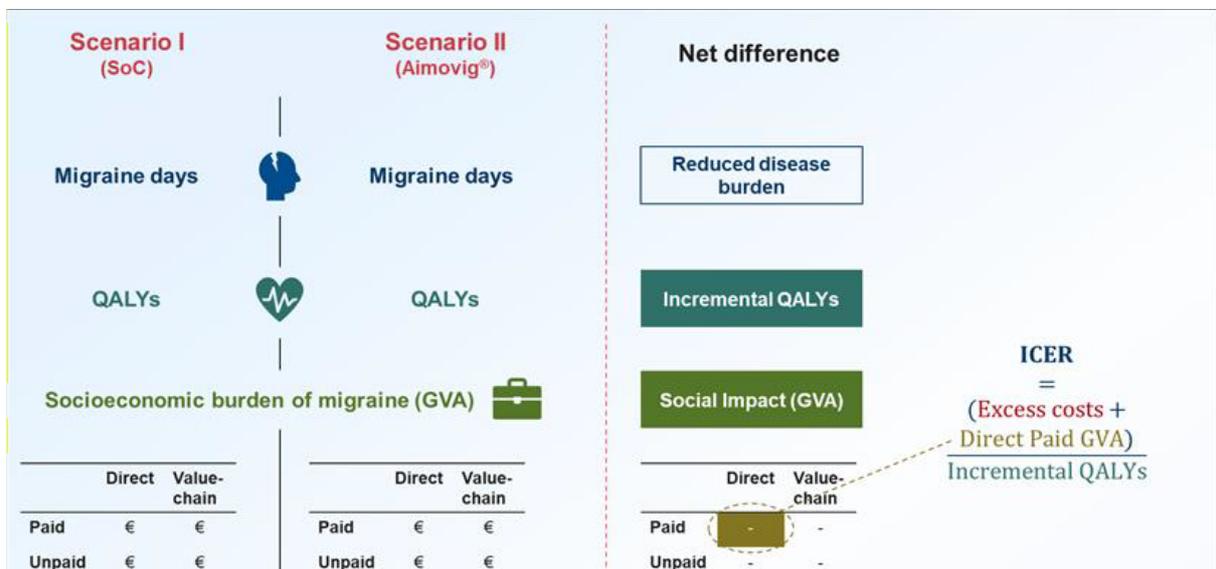
## Economic effects along the value chain

In addition to direct productivity effects, we also considered interdependencies within the economy triggered by initial productivity effects. Building on macroeconomic input-output analysis, an increase in production in one sector is expected to trigger further production of intermediate goods and services as well as incomes in other industry sectors, creating the so-called indirect and induced GVA effects<sup>15</sup>. We calculated the indirect and induced GVA effects of productivity losses using Leontief multipliers<sup>79</sup>. Those were derived from German input-output tables using an input-output model (IOM)<sup>80</sup>.

Indirect effects are effects arising due to the input an industry demands from other economic agents. Order placements result in an increase of economic activity at commissioned agents and their suppliers. This stimulus increases GVA and other economic key figures along the supply chain. Induced effects originate from the expenditure of directly and indirectly generated incomes and the accompanying increase in demand. The combination of indirect and induced effects is called spillover or value-chain effects. The total socioeconomic impact in this study refer to the sum of all three (direct, indirect, and induced) effects<sup>15</sup>.

The following figure represents an illustration of the calculation steps to derive the Social Impact metrics.

Figure 4: Overview of Calculation steps of the Social Impact



### 3.3 Results in a nutshell

Under SoC treatment, 784 million migraine-days occur per year, leading to a productivity loss of EUR 112 billion. This is in line with results reported by Seddik et al. (2020)<sup>81</sup>. Adding Aimovig® as prophylactic migraine treatment reduces these figures to 618 million migraine- days and a productivity loss of EUR 85.5 billion. Our analysis shows that the socioeconomic burden of migraine can potentially be reduced by EUR 26.5 billion in Germany in one year. Forty-seven (47) percent of the avoided productivity loss is attributable to paid work and 53 percent to unpaid work activities. Direct avoided productivity losses in paid work account for EUR 5.8 billion (22 percent). Direct avoided productivity losses in unpaid work amount to EUR 7.2 billion (27 percent). Value chain effects amount to EUR 13.5 billion. The number of migraine patients with at least four MMDs is estimated to be about 6.7 million prevalent patients. The Social Impact per patient is about EUR 3,993 from which EUR 1,867 refer to paid work and EUR 2,125 refer to unpaid work.

We also considered MMD related acute medication use, hospitalization, and costs for Aimovig® treatment. We estimated these at EUR 8.4 billion additional costs for the healthcare system in Germany per year. Once Social Impact and additional healthcare costs are taken into equation, and with the use of broader value dimensions (unpaid work and value chain effects), we can demonstrate a potential monetary net gain of Aimovig® treatment. This is expressed in the value-invest ratio (VIR). From a societal and macroeconomic perspective, each EUR spent on Aimovig® treatment has a potential of avoiding EUR 3.16 welfare or productivity loss for the society.

A probabilistic sensitivity analysis (PSA) with 1,000 iterations was conducted to address uncertainty of input parameters and explore parameter uncertainty effects on model outcomes. The PSA includes clinical inputs, epidemiological data and cost data. Estimates on upper and lower bound values were derived from 95% confidence interval. Based on the parameter’s type, assumptions on the statistical distribution were made.

When testing the model robustness through probabilistic sensitivity analysis, the model consistently yielded positive net excess cost and positive social impact for all 1,000 iterations (Figure 5 and 6). The reduction in productivity losses ranged between EUR 23.7 billion and EUR 27.5 billion EUR (average: EUR 25.6 billion) while the net excess cost ranged between EUR 6.4 billion and EUR 8.7 billion (average: EUR 8.0 billion).

Figure 5: Net excess cost and positive social impact for all 1,000 iterations

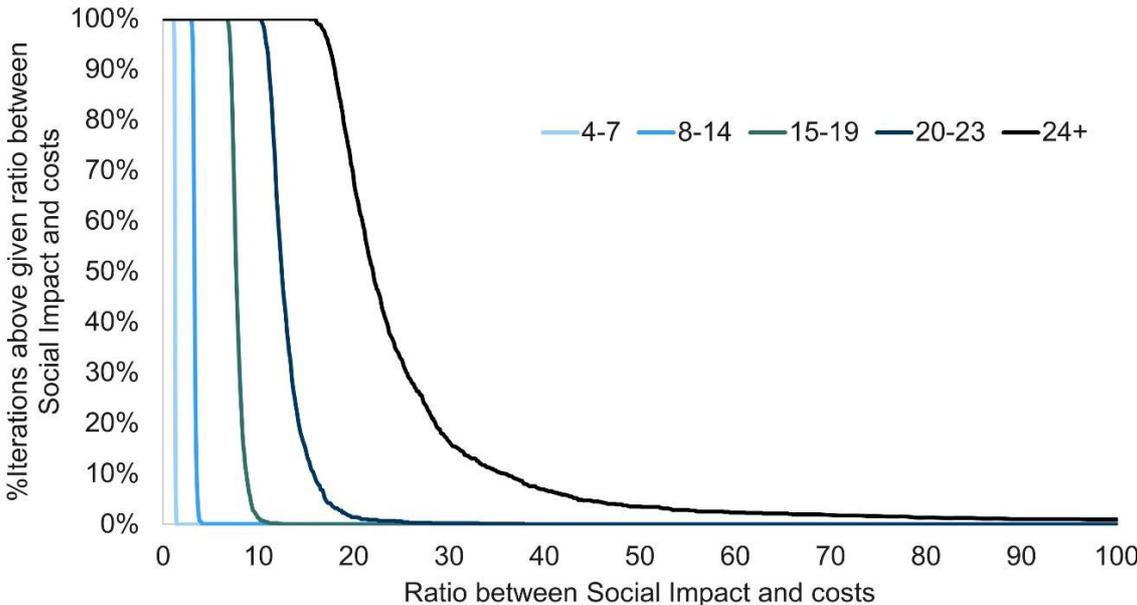
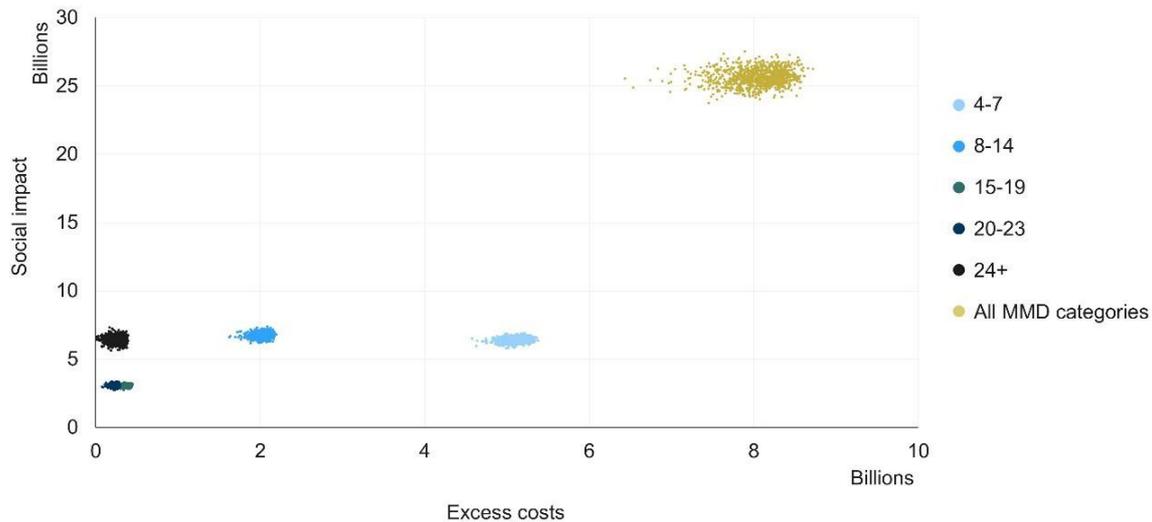


Figure 6: Probabilistic sensitivity analysis



### 3.4 Social Impact approach and the macroeconomic perspective in economic evaluation

The Social Impact approach adds a macroeconomic perspective to the existing evaluations of health technologies. The basis of the Social Impact approach is the existing evaluations or clinical data. By extrapolating evidence from existing evaluations and clinical data to a macroeconomic perspective, it is feasible to model the value of a drug to society in terms of both paid and unpaid work. This is measured in GVA or GDP. In our approach, we value gained productive time for paid and unpaid work with gross value added per working hour and consider value chain (indirect and induced) effects to estimate the wider macroeconomic impact of treatments or innovations. The share of GVA effects for unpaid work and value chain effects compared to solely paid work highlights the importance of considering unpaid and value chain effects as further value dimensions of health innovation from a societal and macroeconomic perspective.

To sum up, the approach provides valuable insights regarding the potential gross value that medical innovation brings to the economy and society in monetary terms. It links evidence from clinical trials and cost-effectiveness analysis with a population model as a basis for the extrapolation of health benefits to an entire patient population. Consideration of unpaid work in the analysis of welfare gains provides a comprehensive view on the gross value of medical innovation. Additionally, it enables different stakeholders, especially the pharmaceutical industry, to shed light on the gross benefits of their medical innovations today and in the future.

The Social Impact, set into background of additional healthcare costs, provides a macroeconomic cost-benefit assessment by showing costs and benefits on a population and macroeconomic level. This adds to the existing knowledge of relative cost-effectiveness of drugs, avoided events, gains in life years or other measurements of health gains. Healthcare decision-makers might benefit from such evidence as it enables the inclusion of additional information on wider societal and macroeconomic impacts in healthcare decision making. As a result, using evidence from common economic evaluations extended by a Social Impact analysis might contribute to better evidence-based decisions.



# 4 Outlook and Limitations

When balancing (often limited) budgets and simultaneously providing access to good health care and medicines, decision-makers invariably face trade-offs. In other words, decision-makers must allocate limited resources efficiently and equitably. Therefore, it is crucial to conduct comprehensive economic evaluations that help decision-makers to make informed resource allocation decisions<sup>82</sup>. In this paper, we attempt to complement the currently used economic evaluations that often adhere to the country specific pharmacoeconomic guidelines. This implies that while productivity costs are not often included, unpaid labor is almost always ignored<sup>83</sup>. By ignoring unpaid activities, economic evaluations miss an important cost (or savings) category and suggesting that these do not play a role in allocation decisions. Many health care technologies are aimed at the elderly populations, who are more involved in unpaid work than paid work, and our examples included show that the avoided losses in welfare are substantial in unpaid work compared to paid work. Therefore, it is imperative not to ignore this category.

Using an approach that incorporates both paid and unpaid labor as well as wider economic value-chain effects is likely to broaden the scope and address various stakeholder perspectives. The approach shifts the discussion towards an understanding of healthcare investments by showing the health and social benefits on a broader scale.

The introduced approach uses GVAs to show potentially avoided productivity losses. GVAs are common economic performance indicators that allow for comparison of estimates across competing investments. The approach allows to assess the Social Impact of innovative medicines by different regions, industry sectors, and fiscal authorities. As a result, the approach covers a broad ground and addresses a diverse group of stakeholders, including manufacturers, employers, working and non-working population, government, and other payers.

However, our approach has several limitations, the majority of which are related to uncertainty associated with modeling future health and socioeconomic events.

For modeling the health outcomes, data from clinical trials are used. While real world data has a lot of advantages to be used as a basis for modeling, the clinical trials have a retrospective view and their external validity (validity of applying the conclusions of a scientific study outside the context of that study) is unknown. We need to add assumptions for future development of epidemiological (e.g., incidences, prevalence, transition probabilities) and socioeconomic developments (i.e., demographic change, age-specific background mortality development).

To monetize the health outcomes (e.g., accrued migraine days), we applied the human capital approach which, in contrast to the friction cost approach, is often reported to overestimate productivity losses. However, the human capital approach is the most commonly used method and differences in estimates between both approaches are marginal when monetizing morbidity outcomes of brief and transient nature<sup>39</sup>. Furthermore, the calculations can be easily adjusted to the friction cost approach for other disease areas.

Though our monetization approach considers unpaid work and value chain effects besides paid work, several important aspects concerning the total societal value might still be missing. A reduced health burden on the population level could have further social implications. A high health burden might lead to anxiety, reduced leisure time activities<sup>84</sup> and avoidance of social events. Moreover, they adversely affect careers and reduce lifetime earnings<sup>85</sup>. Furthermore, the majority of diseases is found to be associated with comorbidities like depression<sup>85,86</sup>. These effects are difficult to measure but point to further individual and public welfare effects. Moreover, further value dimensions of medical innovations are conceivable but were not included in our analysis<sup>87</sup>. If the HC approach is used for valuing paid and unpaid work activities gains, it ignores suitable compensation mechanisms by co-workers and worker replacement, reducing the real paid work loss (in the case on unpaid activities, one

could assume that the affected activity is generally replaced with formal paid caregiving). Thus, the HC approach is often reported to overestimate productivity losses. However, the human capital approach is the most commonly used method and differences in estimates between both approaches are marginal when monetizing morbidity outcomes of brief and transient nature<sup>54</sup>. The FC approach, on the other hand, has been criticized for not considering the value of leisure or household production because this approach assumes no welfare loss or cost when someone who is unemployed becomes employed.

Furthermore, we consider the avoided loss in productivity potential of a healthier population due to a medical innovation, but do not consider potential loss in GVA creation elsewhere (e.g., fewer hospitalizations would potentially reduce GVA creation in hospitals).

Even if it is possible to quantify all associated benefits of a medical innovation, monetary value does not capture aspects such as quality, access, and the broader value to society. Finally, our goal is to show associations, and not causality, as competing efforts (beyond medical innovations) which might also play a role in shaping our outcomes.

Nonetheless, with our approach, we can add evidence to the comprehensive picture in valuing the impact and benefits of medical innovations. Future research in this area could be aimed to derive such unrelated medical costs using standardized methods and estimates across and within specific jurisdictions.



# 5 Conclusion

The Social Impact approach takes a broad view to estimate the potential value a new medicine brings to society beyond the pure clinical scope. Our systematic approach adds a macroeconomic perspective to health-economic evaluations. We use results from existing clinical trials, cost-effectiveness (CE) or cost-utility (CU) models, as well as other health economic evaluations, and layer in a macroeconomic perspective in terms of gross value added (GVA) or gross domestic product (GDP). Thereby, our approach complements existing health economic evaluations, is generalizable to the entire economy and uses straightforward policy measures such as GVA or GDP. As a result of using policy measures, our approach incorporates the multiplier effects, which capture the (positive) externality associated with the medicine or the intervention. We call this the spillover effect or the induced effects beyond the main effect. The approach further incorporates the non-paid impacts. That is, the approach captures the full lifetime effect of an intervention beyond paid work. Recent literature has emphasized the importance of non-paid activities<sup>88</sup> on the societies and we attempt to capture these additional benefits that are not captured in the traditional indirect measures used in CE or CU models. With the Social Impact approach, we propose a systematic way to incorporate productivity and unpaid work in macroeconomic health evaluations.

The Social Impact of medicines captured this way may help to broaden the viewpoint of different stakeholders on the value of innovations. Investing in health is not merely a cost factor, but a driver of growth, employment, innovation and, finally, population health. A Social Impact analysis will help to create an understanding that investments in pharmaceuticals create societal impacts which are measurable in economic terms. Hence, there is a need for not only considering the therapeutic benefits that medical innovations deliver, but also on their contributions towards economic activities and general prosperity.

With this meta study, we aim to set up a framework on how to use the Social Impact analysis for technology assessments in various countries and create a platform for further discussion.

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