FINAL REPORT

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

A Meta Study

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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[1]. Such developments are resulting in important advances and discoveries that are likely to result in improved population health[2,3]. 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[4].

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[5]. 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[6,7]. Improved health triggers economic growth through various channels, such as improving labor productivity, savings or investments in education and other forms of human capital[8–10].

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[11]. 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[12,13]. 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[13]. 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[14–16]. 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* per QALY gained[17–19]. 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[20]. 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[21]. 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 [17,22].

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[23]. The WHO uses DALYs in its Global Burden of Disease Study[24].

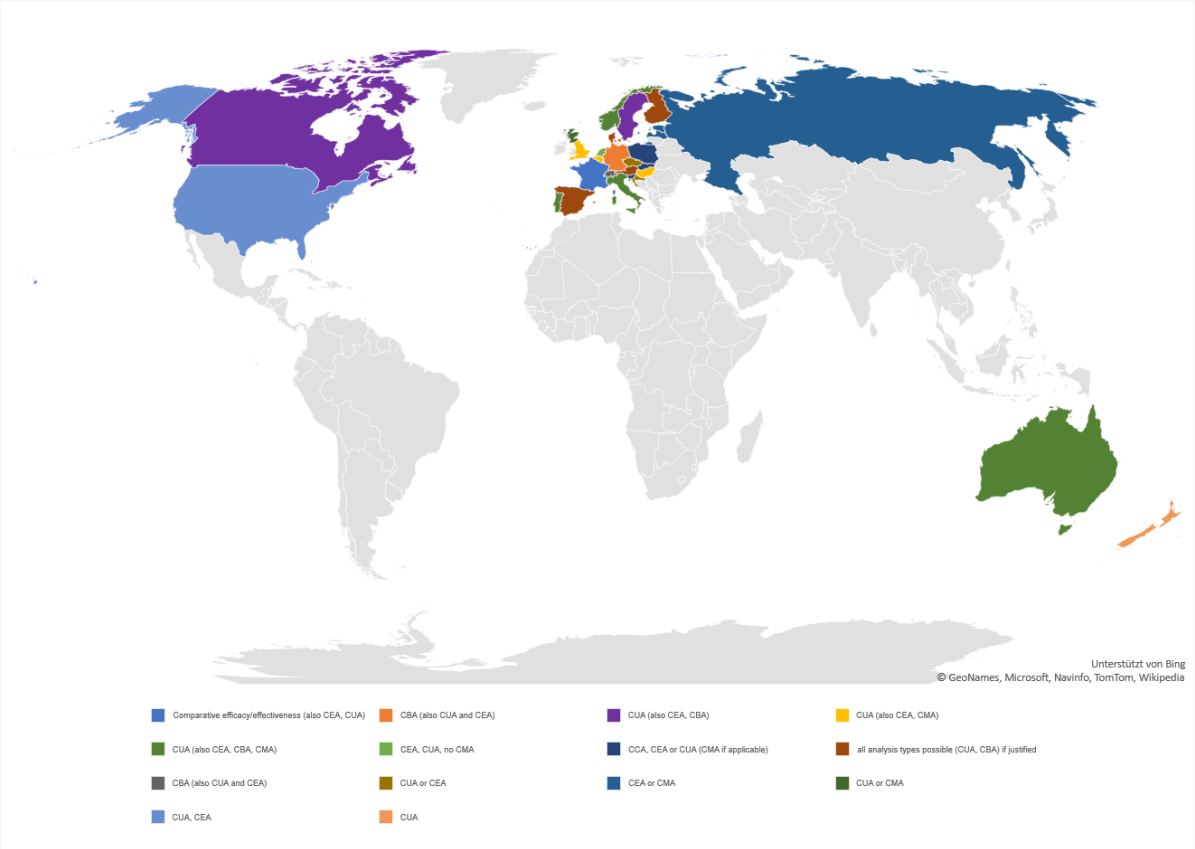
* Cost associated with use of drug relative to a standard of care. Costs generally include administration, adverse events, clinician visits and inpatient hospitalizations.

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 [25]. 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 [26,27]. When assigning a value to QALYs gained, the UK National Institute for Health and Care Excellence (NICE) takes into account end of life situations [28]. Swedish guidelines also adjust the cost per QALY threshold to account for "need" that is related to the disease severity [29].

Nevertheless, in most cases, the use of broader value elements remains implicit and unsystematic [25]. 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) [30], American Society of Clinical Oncology (ASCO) Net Health Benefit (NHB) Assessment Tool [31], the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale [32], the National Comprehensive Cancer Network (NCCN) Evidence Blocks [33], the Institute for Clinical and Economic Review (ICER) Value Assessment Framework [34], and ISPOR Value Assessment Framework [35]. For more detailed information see Misra et al. (2020) which is currently under publication[36].

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[37,38]



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.† 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 [39,40], methods to appropriately capture these value elements [41,42] and empirical work on value elements, for example value of hope[43]. Finally, a wider perspective is critical to value-

† 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.

based pricing‡ as additional information helps payers making investment 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.

	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
Socioeconomic impacts due to better health												
Productivity effects	Macroeconomic Social Impact is not considered yet											
Household production												
Voluntary work												
Spillover effects												

Table 1: Differing methodical supplements for the evaluation of medicines[37,44,45].

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

‡ 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.

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[7,46], 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[47–51]. 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[52]. 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[53] or the friction cost (FC) approach[54]. Both methods can produce widely different results, but both use wages or salaries as a proxy for marginal productivity[55]. 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[49,56]. Furthermore, wages and productivity diverge due to teamwork and unavailability of substitutes, as well as time-sensitivity of the output[57]. Therefore, there are measurement issues regarding market wages as they do not necessarily reflect the true productivity of a worker[58–60].

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[56]. 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.[§] 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)[61].

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[54] or the friction cost approach. The Social Impact is expressed in monetary terms of avoided productivity loses 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

[§] 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.

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.) that is currently under publication[62].

3.2 Social Impact of medicines – a case study: Aimovig®

3.3 Results in a nutshell

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[63]. 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[64]. 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 word 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 (i.e. incidences, prevalence, transition probabilities) and socioeconomic developments (i.e. demographic change, age-specific background mortality development).

To monetize the health outcomes, 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[39]. 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[65] and avoidance of social events. Moreover, they adversely affect careers and reduce lifetime earnings[66]. Furthermore, the majority of diseases is found to be associated with comorbidities like depression[66,67]. 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[68]. 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[54]. 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[69] 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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