MEDICAL AND SOCIAL

ENGLISH SPECIAL 2022

Science & Practice

Information from SBU – The Swedish Agency for Assessment of Health Technology and Social Services

Flaws distort review findings

Systematic reviews can provide more reliable answers than individual studies, offering the possibility of combining findings through meta-analysis. The number of such analyses has increased tenfold in two decades, and confidence in the results is high. However, many of the analyses are not carried out correctly and fail to meet basic quality standards.

Continued, page 2 ▸

SBU – ASSESSING HEALTH TECHNOLOGY AND SOCIAL SERVICES

FRAN_KIE/ SHUTTERSTOCK

Cocksure but dead wrong

THE EARLIEST ADVOCATES for more systematic application of evidence in practice held that the results must be used wisely, judiciously. What does that mean? Taking knowledge and experience into account? Great, but that probably is not enough. History shows that people can be both learned and experienced yet out of their mind. Possessing intelligence? Excellent, but still insufficient. Even the sharpest brains can be applied to witless pursuits.

Judicious use of reliable research findings requires something that Canada-based social psychologists Igor Grossmann and Justin Brienza refer to as *wise reasoning in everyday life*. This is not to be confused with knowledge and intelligence. Rather, it seems to concern an insightful approach to knowledge and experience. According to the authors, four features are involved.

- **First of all:** intellectual humility. This entails recognising the limitations of one's own intellect, openness to reconsidering one's own views and to examining the particulars of a situation before formulating an opinion.
- **Second:** recognition of uncertainty and change; realising that context changes over time and being prepared for the possibility that developments may take unexpected turns; searching for new solutions as problems evolve and consider the use of alternative actions.
- **Third:** perspective-taking of diverse viewpoints – trying to understand the perspectives of others and taking the time to explore divergent opinions before reaching a conclusion.
- **And fourth:** wisdom entails the integration of different viewpoints, so as to balance them one against the other and thereby identify possible compromises between contradictory interests.

BUT CAN WE ACTIVELY develop common sense, can we improve our ability to make sound judgements? Yes, to some extent, say Grossmann and Brienza, building on results from observational and interventional studies. But they also note that preparedness among individuals to reason wisely is also dependent on culture, environmental pressure and leadership.

This all sounds quite reasonable – and if the authors are right, it says something about how we should approach new knowledge. The discursive climate to which we aspire should be open, objective and characterised by the insight that knowledge is neither set in stone nor free from interpretation. We must be ready to embrace new reliable research findings, even when they are in conflict with what we once believed. But that is easier said than done!

Indeed, we find that results that confirm our beliefs are more convincing than those that contradict them. Researchers refer to this concept as *confirmation bias*. The internet is teeming with this type of error (for example 'I don't that it's fake – it's still horrible'). We like, tweet and share whatever fits our prejudices. With cocksure certainty, we compulsively cultivate our preconceived beliefs instead of exploring how things truly relate to each other.

However, anyone who takes the extra time to stop and reflect once again, realises that it is actually wise to remain sceptical of the unproven. And that applies to all of us.

Ragnar Levi
Editor-in-chief

SYNTHESES OF RESEARCH findings occur in many disciplines[1] and have even become a separate field of research. Systematic reviews can provide valuable knowledge, such as in cases where individual studies are too small to provide reliable results. An overall picture is often more accurate.

An important statistical tool for conducting such work is *meta-analysis* (see sidebar). One advantage of combining several observations through meta-analysis is to increase *statistical power*, which makes it possible to demonstrate even minor differences in effect with acceptable statistical confidence – for example, a small but important difference in treatment efficacy between two methods.

BUT THE PURPOSE of meta-analysis is not always to mathematically synthesise the results. Sometimes the purpose is to investigate how the results of different studies vary.[2] In cases where this is the main reason, or when researchers focus on broad generalisations involving many different groups, the analysis may intentionally include studies from completely different categories of participants.[2]

In any event, meta-analysis is a tool that must be correctly and knowledgeably applied. And along with its rapid rise in popularity, a growing number of researchers are sounding the alarm regarding its careless misuse.[3,4] The overall picture will be misleading if aggregation and analysis of the findings of the studies are incorrectly handled. Moreover, because the methodology is so complex, there is also a risk of intentional manipulation.[3,4]

Consequently, systematic reviews using meta-analysis must be subjected to at least as careful scrutiny as other types of research – possibly even more, given that claims of validity are often greater.

For starters, not all compilations that are called meta-analyses truly meet the necessary criteria. For example, simply counting the number of studies that are "for" or "against" an intervention is not a meta-analytical method and may be directly misleading. Nevertheless, this type of "vote counting" is found in reviews.[3] For example, some authors may try to substantiate their assumptions by counting the number of studies with statistically significant and non-significant results. But the finding that significant results outweigh non-significant results hardly constitutes evidentiary support.

One challenge in meta-analysis is to

---

* see e.g. Grossmann I, et al. The strengths of wisdom provide unique contributions… Journal of Intelligence 2018;2:22. DOI: 10.3390/jintelligence6020022

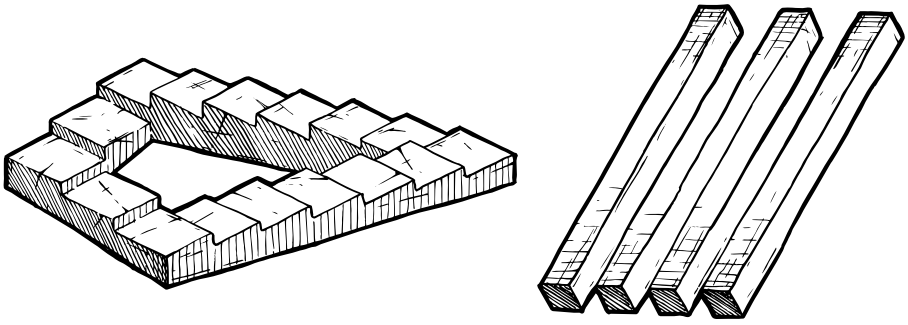
select a suitable model – *fixed* or *random effects*. The choice depends on the purpose of the analysis and how similar the participants in the various studies are deemed to be. If the participants are sufficiently similar, each study´s group of subjects can be thought of as a random sample of the larger population under investigation. In such cases, a synthesis of results contributes to achieving a clearer picture of the population at large, and the *fixed effect* model is used. However, should the studies differ to the point that participants can be considered to represent different populations, a *random effects* model should be used instead. In the latter case, the analysis results correspond to an average effect across all populations, which of course may deviate from the actual effect in a single population.

Meta-analysis also requires a review and ranking of data before they are synthesised. Well-established statistical methodology must be used when calculating effect size, weighting results from different studies and addressing any heterogeneity in the data.

Results are often weighted based on the width of the confidence intervals. The purpose is to be able to distinguish the uncertainty in individual studies from the uncertainty associated with the collective results.[2] Without weighting, it becomes difficult to assess how "robust" the aggregate results of the meta-analysis are as a whole, and how dependent they may be on certain included studies. Weighting also prevents small studies from having too much influence on the collective results (in the *fixed effect* model), which can otherwise be a problem – for two reasons.

ONE IS THAT small studies are inherently more sensitive to *random errors*. The fewer observations made in a study, the greater the latitude for randomness. Studies with few participants are more sensitive to random effects – the results will vary more than in larger studies.[2]

Secondly, it is known that publication of small clinical trials with negative outcomes tend to be delayed or, in the worst-case scenario, fail to be published at all, in which case the findings remain unknown. This skews the overall picture of treatment efficacy, resulting in *publication bias*.[2] In fields of research dominated by small treatment studies, the overall picture of the beneficial effects of treatment therefore tends to be exaggerated.



BABICH ALEXANDER / SHUTTERSTOCK

Formerly a scarcity in the research literature from the 1990s, scientific journals are now veritably flooded with results from meta-analyses, many of which have been criticised as redundant, erroneous, or both.[4,5] The tendency for researchers to be opinionated regarding substantive issues may bias results, but this is hardly unique to meta-analysis. As with other approaches, researchers must make choices which may affect results.[4] Researchers must decide what types of studies to cover, how old they may be and what languages to include. The quality criteria used to cull studies may also vary in regard to both stringency and application.

FOR THIS REASON, the scientific community must remain vigilant that researchers disclose their choices and explain their process. Authors must openly and clearly explain and motivate their decisions (transparency in reporting) in order for a meta-analysis to be considered reliable.

Technological developments in the field, such as machine learning and artificial intelligence, pose both opportunities and challenges. Broad access to advanced statistical analytical tools allows an ever-growing number of researchers to carry out increasingly complex calculations – without necessarily themselves possessing the knowledge or statistical expertise to do so. The more convoluted the analyses, the more difficult it becomes for researchers, reviewers and others to discover errors and detect bias.

One example is *network meta-analysis* – an advanced analytical method that is becoming increasingly common and which can easily yield erroneous findings.[6] This type of meta-analysis compares three or more treatments by combining both direct and indirect comparison results from various trials. While traditional meta-analysis only makes ▶

META-ANALYSIS

Statistical analysis method to quantitatively synthesise findings from primary studies of the same diagnostic method or intervention. The method is frequently used in the context of systematic reviews and follows a previously determined process.

An exhaustive literature search is used to obtain all available research concerning the questions to be answered. The material is sorted and culled, after which it is reviewed according to previously determined criteria and then synthesised to produce an aggregate result with associated confidence intervals.

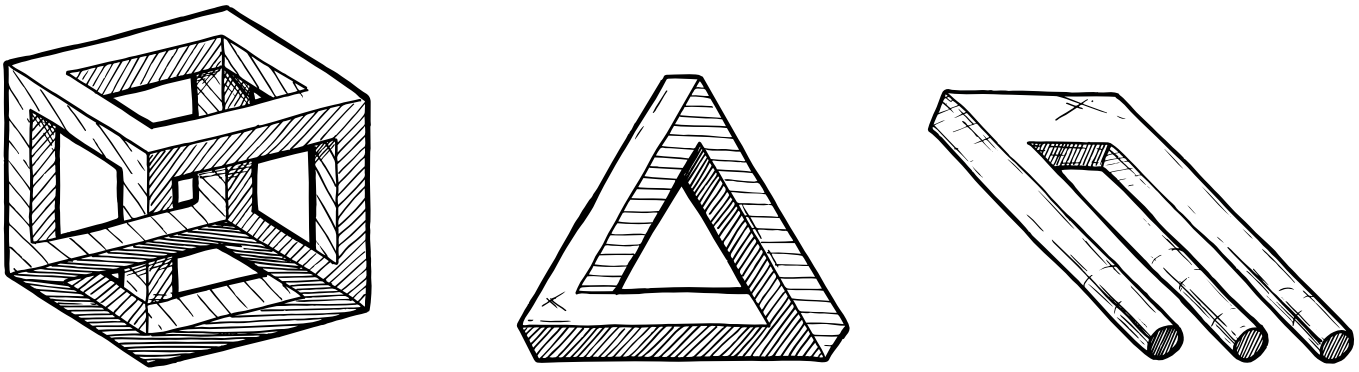
Larger studies with greater numbers of participants and clinical events are given higher weight in the final analysis.

The analysis provides an overview of the available results and how consistent they are. Historically, the first meta-analysis was carried out in 1904, but the method did not become established until the 1990s.

Meta-analysis itself does not inherently assess the risk of bias; instead this is estimated later in a separate evidence grading process.

INTERNATIONAL STANDARDS

- **AMSTAR** – checklist for assessing the methodological quality of systematic reviews at the overarching level (not for individual outcomes)
  https://amstar.ca
- **ROBIS** – tool for assessing the risk of bias in systematic reviews
  https://www.bristol.ac.uk/population-health-sciences/projects/robis/robis-tool/
- **MECIR** and **MECCIR** – Standards for the conduct and reporting of systematic reviews from Cochrane and Campbell Collaboration
  https://community.cochrane.org/mecir-manual
- **PRISMA** – basic requirements of scientific journals and publishers on how to report systematic reviews and meta-analyses
  http://www.prisma-statement.org
- **RAMESES** – UK project to produce standards and tools in a qualitative approach to assess the reporting of systematic reviews
  https://www.ramesesproject.org



BABICH ALEXANDER / SHUTTERSTOCK

▶ *Cont'd from page 3:*
direct comparisons between interventions, network meta-analysis also makes indirect comparisons – including interventions that were never tested side by side within one and the same trial. In order to also compare interventions that were never tested directly head to head, effect estimates from trials that share a common comparator are used. For example, when A vs B is the comparison of interest, randomised trials on A vs C and on B vs C are used as indirect evidence. A large network meta-analysis may include more than 20 comparisons.

THE EXTENT TO which use of network meta-analysis can at all be considered appropriate once again depends on how similar the studies are. Such an assessment requires knowledge of the subject and affects choice of statistical methodology – where the options are many. Various draft review templates for network meta-analysis have been published.[7-10]

An array of pitfalls must be avoided when conducting and interpreting meta-analyses, ranging from simple to highly complex. While meta-analysis has proven valuable as a statistical tool, it is often used incorrectly. A large proportion of published analyses have been deemed substandard.[4]

It is paramount to remember that meta-analytic tools in themselves are by no means a guarantee of quality. ◆ **RL**

References

1. Gough D, et al. Syst Rev. 2020;9:155.
2. Gurevitch J, et al. Nature 2018;555:175-82.
3. de Vrieze J. Science 2018;361:1184-8.
4. Ioannidis JPA. Milbank Q, 2016;94:485-514.
5. Leclercq V, et al. BMJ Open 2020;10:e036349.
6. Anttila S. SBU, Vetenskap & praxis, 2018:(1-2):12-3.
7. Nikolakopoulou A, et al. PLoS Med 2020;17:e1003082.
8. Puhan MA, et al. BMJ 2014;349:g5630.
9. Jansen J, et al. Value Health 2014;17:157-73.
10. Brignardello-Petersen R, et al. BMJ 2020;371:m3907

WELL-CONDUCTED SYSTEMATIC REVIEWS – IDENTIFYING CHARACTERISTICS

Study choice matches the aim

- The aim of the review was determined in advance, as were criteria for inclusion of studies.
- Selection of studies is commensurate with the question to be answered by the review.
- The selection criteria are clear and take into account the currency, size and quality of the studies, as well as relevance of outcomes.
- The selection takes into account the source, e.g. type of publication, language and availability of raw data.
- A list of the studies that were not included in the compilation.

Thoroughness of literature search

- The search covers suitable databases and other important sources.
- Search terms and phrases are formulated to identify the greatest possible number of relevant studies.
- Constraints regarding year, type and language of publication are clearly and appropriately disclosed.
- Special measures were taken to minimise the risk of biased study selection. Experts in the field were consulted.

Critical review of studies

- Special measures were taken to avoid errors when collecting data from the studies. Participants, interventions and treatments are described in detail.
- Review authors have sufficient information and knowledge to interpret the data.
- All relevant outcomes are included and reported in the compilation.
- A structured approach with appropriate criteria was used to assess the risk of bias in the results, and the conclusions are clearly supported.
- Special measures were taken to avoid erroneous assessment of the risk of bias and to resolve disagreements regarding the assessment.

Accuracy in compilation

- The review includes all studies that meet the predetermined criteria and describes the relevance of all studies in relation to the question that the review aims to answer.
- All predetermined analyses are presented and deviations, if any, are explained.
- Choice of analytical model is justified. Studies from which the findings are compiled are deemed to be sufficiently similar concerning question to be answered, design and outcome measures. Disparities among studies, if any, are appropriately managed.
- Aggregate results are sufficiently robust to stand up to sensitivity analysis, and the risk of biased publication of studies has been taken into account and assessed using different methods.
- The weaknesses identified in the studies are taken into account in the conclusions of the review. The risk of bias in these conclusions and in the interpretation of findings by the authors were appropriately described and addressed. The authors do not present only statistically significant findings, but report all outcomes. Sources of funding for the review are disclosed.

Sources: Whiting P, et al. ROBIS: A new tool ... J Clin Epidemiol. 2016;69:225-34 and SBU's Handbook

Bridging the science – policy gap

Researchers and policymakers have completely different roles – their remits cannot replace one another. But there is growing consensus that the gap between them must be narrowed if society is to cope with the challenges of health and welfare.

The relationship between science and policy is far from simple. Many researchers have described the problems associated with the divide between them – *the science-policy gap*.

While science is devoted to the pursuit of knowledge, policy pertains to the discussion of what goals should be achieved based on values and available resources. While their roles must be kept separate, collaboration between them should be improved, according to critics.[1] Many call for a more evidence-based and systemic decision-making process – especially with respect to complex and drastic threats to the future such as dangerous infectious diseases, exhausting the planet's resources and climate change.[2] But bridging the gap between science and policy poses several challenges.

A FIRST CHALLENGE is related to the super-specialisation and fragmentation of both science[3] and policymaking,[4] while many problems remain intertwined. Human health and welfare depend on more than just healthcare and social services policy. Other factors such as education, employment, finances, living environment both at home and at work, transportation and social relationships also have an impact.

Although the issues in question are interrelated, the responsibilities, budgets and planning rarely are. Silo mentality, turf guarding and inadequate oversight in both academia and politics may become devastating given the complex nature of interactions between lifestyles, living conditions and human health.

THE NEXT PROBLEM is to deal with incomplete knowledge and scientific uncertainty.

Policymakers, including their staff who draft the policies, may lack knowledge of relevant research findings. They may not have the knowledge to determine whether the findings are reliable and how they should be interpreted. Sometimes there are no scientifically sound answers to current policy questions;[5] for example, in cases when it is difficult or impossible to test them experimentally.[6] Many research studies are focused on narrow questions, without considering the knowledge gaps where the need for an improved decision-making basis is greatest.[7,8] Politically relevant issues may not be clearly defined. Addressing uncertainty requires extrapolation or generalisation, based on assumptions and models.

A third challenge is that researchers and policymakers often have different time horizons. Policy often moves quicker than science. Social issues are sometimes difficult to predict and may rapidly become urgent. Previously forgotten issues can suddenly become highly relevant. Politicians often find themselves forced to make quick decisions based on preliminary knowledge and forecasts, while researchers prefer to carefully test new hypotheses and slowly build on existing knowledge.[9] These disciplines cannot always be synchronised so that current and reliable data are available precisely when a decision is to be made.

When researchers are queried in surveys whether they communicate with policymakers, many respond that they would like to do so, but do not have the time.[10] In a 2018 Swedish survey of 18,000 researchers and postgraduate students, two-thirds of the 3,700 researchers who responded said that policymakers and politicians are the single most important group with which to communicate. At the same time, however, this target group ranked only fifth among those with whom the respondents had actually communicated in the past year.[10] The reported lack of time may in turn have many causes. In international studies[11], researchers and policymakers also point to the importance of networking opportunities, access to information, organisational support, mutual understanding of each other's roles and work processes, as well as costs and finances.

IT IS ALSO not a given that all policymakers care about research results, or that researchers are interested in policy problems. After all, their motivations are different.[2] In extreme cases, they directly distance themselves from each other's work – known as "fact resistance" or "contempt for politicians" – or they cherry pick pieces of information that support their own views and agendas. ▶

WHO IS DANNY / SHUTTERSTOCK

► *Cont'd from page 5:*
The use of scientific knowledge by policymakers can be divided into three categories – instrumental, conceptual and symbolic use.[12] In instrumental use, knowledge directly guides the decisions to be made. Conceptual use is more indirect: knowledge influences the long-term attitude of politicians and officials concerning various problems and how they should be addressed. Finally, in symbolic use, policymakers are merely seeking legitimacy for a decision that has already been taken. In practice, it can be assumed that many policies combine elements from all three categories. Also policymaking often requires adapting the general knowledge from research to a specific situation in a particular context.

RESEARCHERS, FOR THEIR part, may have no interest in policy issues or ideologically based priority-setting. They may fail to realise that decisions are not based solely on knowledge and that policy is also shaped by what is possible to get through the political decision-making process. Although the "third mission" (collaboration and outreach) of public universities and higher education institutions in Sweden includes making use of research findings,[13] there is also significant confusion among researchers concerning its implications.[14]

While many point to an urgent need for better collaboration between research and policy, other authors argue in favour of clearly separating the knowledge-generating role of research from policy practices. Both are necessary, but they are not interchangeable. For example, the democratic process may suffer in the case of expert rule where knowledge replaces policy, or where dogmatic policy masquerades as knowledge.[15] Uncritical deference to all claims perceived as expert opinion is also problematic.

SINCE POLICY DECISIONS are prepared by officials, this group also play a key role in the dialogue between researchers and politicians. In their capacity as intermediaries, they must have sufficient knowledge to avoid misinterpretation of research findings. They must be able to understand the basis for decisions so that politicians can comprehend the ideological implications, as well as what is feasible in terms of values and acceptance by voters.

Despite the pitfalls and challenges, many agree that the gap between what research shows and what policy dictates should narrow. Well-informed decisions concerning health and welfare - evidence-informed policy – are based insofar as possible on relevant, unbiased and comprehensive factual basis, and sufficient knowledge of likely effects. ◆ **RL**

References

1. Widman Lundmark L, et al. "Var är forskningen i de politiska manifesten?" Opinion piece by representatives of 61 knowledge organisations in the newspaper SvD 2018-09-09.
2. Martin K, et al. Overcoming the research to policy gap. The Lancet Global Health 2019. https://doi.org/10.1016/S2214-109X(19)30082-8
3. Vetenskapsrådet. Forskningsöversikt 2019. Medicin och hälsa. Downloaded from www.vr.se
4. Marmot M, et al. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet 2008;375:1661-9.
5. Science Advice for Policy by European Academies. Making sense of science for policy under conditions of complexity and uncertainty. Berlin: SAPEA, 2019. https://doi.org/10.26356/MASOS
6. Brännmark J. Evidensbasering i politiken. I: Sahlin NE [red]. Vetenskap och beprövad erfarenhet: Politik. Lund: Lunds universitet, 2018.
7. Chalmers I, et al. Avoidable waste in the production ... of research evidence. Lancet 2009;374:86-9.
8. Glasziou P, et al. Research waste is still a scandal, BMJ 2018;363:k4645.
9. Bell C, et al. Providing policy makers with timely advice: The timeliness-rigor trade-off. World Bank policy research working paper No. 7610, 2016.
10. Bohlin G, et al. Forskares syn på kommunikation och öppen vetenskap. Nationell enkätundersökning 2019. VA-rapport 2019:8.
11. Oliver et al. A systematic review of barriers to and facilitators of the use of evidence by policymakers. BMC Health Services Research 2014;14:2.
12. Knaggård Å. Vetenskaplig kunskap i politiken. I: Sahlin NE [red]. Vetenskap och beprövad erfarenhet: Politik. Lund: Lunds universitet, 2018.
13. Högskolelag 1992:1434. Downloaded from https://lagen.nu/1992:1434#K1P2S2
14. Bohlin G, et al. Forskares syn på forskningskommunikation och öppen vetenskap. VA-rapport 2018:1.
15. Torgerson D. Between knowledge and politics: Three faces of policy. Analysis & Policy Sciences 1986;19:33-59.

Health economists search for ways to stretch healthcare budgets

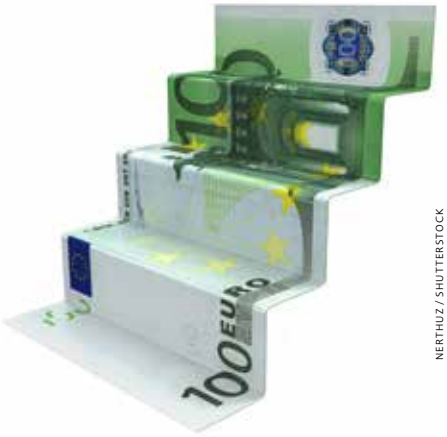
When the need for healthcare and social services is great, but resources are running low, it is especially important to focus on measures that provide the most efficient return for the money. SBU's health economists work to inform decisions by comparing the benefits of various interventions with their costs.

When demand for healthcare and social services exceeds what society can provide, resources must be wisely managed. There simply is not enough to go around. Economists commonly refer to *opportunity cost* to describe the value or benefit of the opportunity given up each time a decision is made to spend limited resources on a different option, ie, the "sacrifice" that is incurred.

Policymakers constantly set priorities among different options. But the huge expenses during the COVID-19 pandemic brought such issues into the spotlight. What interventions must be eliminated to make ends meet? Where should the resources be obtained in order for healthcare and social services to provide care for these patients?

In Sweden, priorities in publicly funded health care must be set based on the *ethical platform*, which was adopted by the Swedish Riksdag in 1997. It encompasses the ethical principles of human dignity, needs and solidarity, and cost-effectiveness.

When SBU conducts a *cost effectiveness* analysis, the focus is on what interventions provide the most health for the money. According to the corresponding principle of the ethical platform, health care has a duty to utilise its resources as efficiently as possible.



NERTHUZ / SHUTTERSTOCK

This discipline of knowledge is called *health economics* and is a subdiscipline of economics. This field applies knowledge and theories about human behaviour and values, as well as the organisation of health care and its financing. Health economics usually deals with comparing various interventions with regard to their costs and effects on health and quality of life. Similar assessments are also conducted regarding interventions within social services, although in such cases the effects are not limited to health.

Cost-effectiveness analysis entails comparing costs and outcomes of two or more interventions. An intervention characterised by both lower costs and better outcomes than a different alternative is considered to be *dominant*. In such cases, choice of intervention is simple from the standpoint of health economics. However, in many cases, more effective interventions are also more expensive. The health economist will then want to determine whether the more effective intervention is worth the increased cost.

The methodology used to measure and analyse cost-effectiveness may vary. The outcome measure preferred by health economists is known as *quality-adjusted life-years* (QALYs). This measure considers not only how long a patient with a particular medical condition lives, but also the quality of life during this period.

Quality of life, also known as QALY weights, is usually represented on a scale ranging from 0 to 1, where 0 corresponds to death and 1 designates perfect health. In order to indicate how treatment effects both length of life and quality ▸

▶ *Cont'd from page 7:*
of life, the number of life-years gained is multiplied by the estimated average quality of life. For example, a treatment that prolongs life by an average of five years with an average quality of life weight of 0.7 yields 5 x 0.7 = 3.5 QALYs.

QALYs are widely used in health economics, regardless of what disease is under analysis, as a universal measure of health outcomes for different conditions and treatments. The idea is to be able to compare how much health can be achieved for a given cost, even when analysing completely different treatments and conditions. Such comparisons, however, require that the estimate of quality of life concerning different conditions, i.e. the QALY weight to be used, is completely accurate and universally valid. This is one of the factors that determines whether or not a health economic calculation represents a correct portrayal.

The QALY weight can be calculated using either direct or indirect methodology. Direct methods include in part *standard gamble* and *time trade-off*, where people are asked to choose between different scenarios, and in part visual analogue scales, where people rate the state of their health on a scale from best possible to worst possible. In contrast, indirect methods rely on responses to questionnaires called *quality of life instruments* (e.g. EQ-5D, SF-6D and HUI-3). The responses are converted into QALY weights using a scoring system known as a *tariff*, which in turn was obtained using one of the direct methods.

WHEN REVIEWING HEALTH economic analyses, it is important to assess how the QALY weights were calculated, based on the quality of life instrument and valuation system used. It is important to know the category to which the people who completed the questionnaire belonged – for example, whether the quality of life associated with the condition has been assessed by the general public (i.e. hypothetically by people with no personal experience of the condition), by subject matter experts (i.e. people with professional knowledge and experience), or by people or patients who actually have the condition. Quality of life is often rated higher by those who actually live with the condition than by the general population, who can only imagine what the situation must be like.*

HEALTH ECONOMISTS USE many types of analytical methods; see the sidebar. Selection of methodology depends on the question the analysis must answer, but also on available data. When health care most choose between two equally effective interventions that entail equivalent risks, a *cost-minimisation analysis* may serve the purpose well. When the choice comes down to alternative methods that mainly affect mortality, in some cases a *cost-effectiveness analysis* using life-years as an outcome measure may suffice. If the concern is with treatment of chronic conditions that pose no direct threat to life, it will be necessary to consider impact on quality of life as well. The is when a *cost-benefit analysis* comes into play.

The outcome when comparing health economic aspects of two interventions is often presented as an *incremental cost-effectiveness ratio* (ICER) – the ratio between difference in cost and difference in effectiveness. This ratio denotes the cost of gaining one additional unit of effect (e.g. a life-year gained) when choosing one intervention over another.

When discussing the ICER of an intervention, health economists usually consider it in relation to the amount of money that society has seemed willing to pay for a particular unit of effect, such as a QALY. This amount is referred the *willingness-to-pay threshold*. Although this threshold can be analysed using scientific methodology, the actual value is determined by societal values and policymakers – not by researchers.

THERE ARE VARIOUS ways to define and study threshold values, but no definitive threshold value has been determined for Sweden. According to the health

KRZYSZTOF BUBEL/SHUTTERSTOCK

* Aronsson M, et al. Differences between hypothetical and experience-based value sets for EQ-5D used in Sweden: Implications for decision makers. Scand J Public Health. 2015;43:848-54. .

economics literature, there is in fact considerable variation – one study estimated that individuals are willing to sacrifice between SEK 150,000 and 350,000 in consumption in order to gain one additional QALY, while another came up with an amount of SEK 2.4 million. In line with the ethical platform for priority-setting adopted by the Riksdag, willingness to pay within the Swedish healthcare system is also influenced by other factors, such as severity of the condition, rarity of the disease and magnitude of the treatment response, as well as the reliability of the health economic analysis.

THE COSTS OF the disease and its care are usually divided into *direct* and *indirect costs*. Direct costs are incurred as a direct result of care and treatment – staff, premises, equipment and costs attributed to the patient. Indirect costs refer to resources that are indirectly lost as a result of the disease or treatment, such as impaired ability to work or loss of production, in cases where people are unable to work due to the disease or the treatment. Loss of production also includes what is known as sickness presence, when the individual works but is less productive than previously because of illness or injury. The types of costs included in a health economic analysis depend on the type of intervention being assessed, and the perspective to be applied – for example, a health care perspective or a societal perspective. The principle of human dignity contained in the ethical platform also influences what costs are included.

Agencies such as SBU view the situation from a societal perspective to show the total costs and effects for society at large, not just for a particular sector. Costs and effects must be taken into account regardless of where they arise, yet it is common practice to describe how costs and effects are distributed among the different actors. How indirect costs affect cost-effectiveness is also addressed.

WHEN SBU EVALUATES health economic aspects, the first step is usually to carry out a review of published health economic studies. The Agency reviews both *empirical studies*, those which are designed to gather data on both costs and effects within the context of the same study, and *modelling analyses*, which combine efficacy data from clinical trials (or meta-analyses of such trials) with data on costs and risks of disease from other sources.

Model analyses require certain assumptions and cannot replace empirical studies. They are primarily used in an attempt to predict costs and effects over a longer timeframe than that covered by current studies. They are also used when efficacy studies or data concerning costs and QALYs are unavailable. The most common methods used in model analysis are called *decision trees* and *Markov models*.

One important issue when reviewing health economic studies is to consider the risk of inappropriate influence on the results, such as certain cases of industry sponsorship. Since the calculations are often carried out in other countries, it also becomes necessary to ascertain whether the data that were used appear to deviate significantly from Swedish conditions, and whether Swedish data would have yielded a similar result. Countries may differ significantly in questions such as organisation, costs, disease prevalence, mortality and quality of life.

MODELS MUST BE subjected to thorough *sensitivity analysis* in order to ascertain the reliability of the results. In this way, authors must demonstrate how robust the results are when certain conditions, data and assumptions change. For example, they may investigate the effect on results when certain outlying data are discarded or replaced with alternatives. Sometimes a *probabilistic sensitivity analysis* is conducted in which the uncertainties associated with different values and assumptions are concomitantly analysed in order to determine the combined uncertainty.

The current health economic literature cannot always provide an answer to the policy questions posed by SBU projects. In such cases, SBU can team up with subject matter experts to conduct its own analyses of cost-effectiveness, based on clinical studies and Swedish cost data.

CLASSIC ANALYSES IN HEALTH ECONOMICS

Cost-minimisation analysis – compares costs for different interventions where the outcome is expected to be identical

Cost consequence analysis – compares costs and effects of different interventions, including multiple outcome measures

Cost-effectiveness analysis – compares the costs and effects of different interventions, with effects expressed in a specified unit, such as life years

Cost-benefit analysis – compares costs and effects of different interventions, with effects expressed in quality-adjusted life years (QALYs)

Cost-benefit analysis – compares costs and effects of different interventions, with effects expressed in monetary terms, such as SEK

In some cases, it may be sufficient for the agency to study the costs associated with different interventions in relation to efficacy studies in order to be able to assess the cost-effectiveness of the interventions. In other cases, complete model analyses may be necessary.

The reliability of the results is of course a key issue when conducting health economic calculations. The reliability of health economic outcomes (e.g. days of care) in randomised studies can be evidence-graded, just as with medical outcomes. When it comes to cost-effectiveness, the problem becomes more difficult since different outcomes are aggregated.

In health economics, as in other fields of research, it is paramount that numbers are never perceived as being more reliable or accurate than they actually are. ◆ **RL**

Reading tips

- Socialdepartmentet (1995), Vårdens svåra val. Prioriteringsutredningens slutbetänkande, SOU 1995:5.
- Socialdepartementet (1996/97), Prioriteringar inom hälso- och sjukvården. Proposition, 1996/97:60.
- SBU:s metodbok, www.sbu.se/metodbok

Researchers must give the full picture

Human life and health are at stake when clinical research findings are presented in an incomplete, obscure or misleading manner. Many countries are therefore attempting to remedy the problems – despite considerable obstacles.

When researchers present their findings, they must often be selective, but the overall picture must still be accurate. All relevant studies must be openly reported with their main findings highlighted, regardless of whether they support or undermine a particular intervention.

This describes the ideal scenario. However, selective and biased reporting of results is in fact a major problem in treatment research.[1] Studies that fail to support the tested intervention clearly and through statistical reliability are sometimes published after considerable delay - or in the worst case scenario, not at all. Moreover, papers with unfavourable or unclear results rarely appear in prestigious journals and are cited less frequently by other researchers. Such skewing in the literature is referred to as *publication bias* and provides policymakers, professionals and patients with an overall distorted view concerning the benefits of treatment.[2] Distorting the overall picture in this way may influence healthcare decisions and lead to misallocation of scarce resources.

Such bias may also be noted in how researchers select what results to report from individual studies, known as *outcome reporting bias*.[2] For example, authors may choose to move the focus from the central outcomes in the study to more peripheral outcomes that have demonstrated greater impact. The consequence is an exaggeration of treatment effects.[3,5] It is therefore considered highly inappropriate for researchers to use their own findings to reformulate what was initially a central research question into one that is peripheral, and thereby instead give greater weight to less important outcomes. For example, if a treatment does not affect morbidity and mortality, and these were the central issues addressed by the study, the author of the article should not focus on isolated promising lab results.

Biased publication of findings, also referred to in the literature as *spin*, is nothing new in research.[4] Many possible reasons have been proposed,[5] including that manufacturers and sponsors want the research to benefit sales of their products. Another possible reason is that scientific journal editors and researchers are looking for exciting results that will draw attention and benefit their business and career.

However, biased publication is not the only reason that certain research results remain in the shadows. Some research reports are difficult to access. *Grey literature*, which exists alongside traditional scientific journals, sometimes remains invisible in mainstream research databases.[6] This category may include unpublished corporate information, academic theses from various countries, government studies and reports from agencies, authorities, regions and municipalities. Moreover, many scientific journals still charge hefty fees and lock articles behind paywalls, despite international and national *open access initiatives*.

However, many countries are fighting for greater transparency, especially in regard to publicly funded research, and for full disclosure of such results. The European Commission is working to achieve *open science*, including by facilitating access to and re-use of research data and findings.[7] According to the Commission, open science should promote transparency and publicly available findings.

The UK's "Make it Public" strategy, launched by the National Health Services (NHS) in 2020, aims to ensure open access to research information by improving ▶

LISA VLASENKO / ISTOCK

4X6 / ISTOCK

▶ *Cont'd from page 10:*
registration of studies, information to participants and reporting of results.[8] The NHS Medical Research Authority has adopted a ten-point action plan. See sidebar.

CRITICS IN SWEDEN have argued for clarification of requirements to be met by Swedish researchers when publishing final reports from clinical trials.[9] In January 2021, the organisation Transparimed and Cochrane Sweden issued proposals[9,10] pertaining to this area, including that Swedish authorities and research funders should endorse and adopt the World Health Organisation's statement[11] concerning public access to clinical research results. In conjunction with the pandemic, the Swedish Research Council specifically endorsed[12] the British research fund Wellcome Trust's call[13] for researchers, journals and research funders to ensure rapid sharing and open access to results and data relevant to management of the coronavirus.[14] In this context, the Swedish Research Council also recommended that publicly funded research data should be published openly online within a reasonable period after publication of the results – with the exception of cases such as copyright-protected data.[12]

As long as the affected policymakers, researchers, professionals and patients are only allowed access to selected portions of the scientific evidence, the risk that the overall picture will be biased remains. This situation could allow treatments that are actually ineffective or even harmful to erroneously be perceived as beneficial or cost-effective. ◆ **RL**

BRITISH TEN-POINT PROGRAMME

1. Be clear about what is expected of sponsors and researchers and what they can expect
2. Support good practice through guidance, education and clear communication
3. Maintain a high-quality, interconnected research approvals system
4. Remind researchers and sponsors when reporting is due
5. Work with research funding bodies, other regulators and publishers to make sure that expectations around research transparency are consistent and aligned
6. Reward and celebrate good practice and highlight poor performance
7. Take action where researchers and sponsors do not fulfill their research transparency responsibilities
8. Ensure that all clinical trials conducted in the UK are registered, unless the sponsor has permission to delay this to a later stage
9. Publish or share accessible information about individual studies and their findings
10. Work with partners to ensure that information for the public is easy to understand

Source: NHS Health Research Authority, 2020

References

1. Dwan K, et al, for the Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE 2013;8:e66844.
2. Page MJ, et al. Investigating and dealing with publication bias and other reporting biases in meta-analyses of health research: A review. Res Syn Meth 2021;12:248-59.
3. Bruckner T. Clinical trial transparency: A guide for policy makers. Transparency International, et al, 2017. Downloaded from https://www.transparimed.org/reports
4. Boutron I, et al. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. JAMA 2010;303:2058-64.
5. Chiu K, et al. "Spin" in published biomedical literature: A methodological systematic review. PLoS Biol 2017;15:e2002173.
6. Schöpfel J. Towards a Prague definition of grey literature. Twelfth international conference on grey literature: Transparency in grey literature. Downloaded from https://archivesic.ccsd.cnrs.fr/sic_00581570
7. EU Commission. Open Science Policy Platform Recommendations, https://ec.europa.eu/research/openscience/pdf/integrated_advice_opspp_recommendations.pdf
8. NHS Health Research Authority. Make it public. Transparency and openness in health and social care research. July 2020. Downloaded from https://www.hra.nhs.uk/
9. Engelmark S. Stora brister i rapporteringen av kliniska studier. Tidningen Curie, Vetenskapsrådet, 2021-01-13. Downloaded from https://www.tidningencurie.se
10. Bruckner T. Results are missing for over two hundred drug trials involving Swedish patients. Article downloaded from https://www.transparimed.org/single-post/results-are-missing-for-over-two-hundred-drug-trials-involving-swedish-patients
11. WHO, https://cdn.who.int/media/docs/default-source/clinical-trials/ictrp-jointstatement-2017.pdf
12. Vetenskapsrådet. Dela forskningsdata och resultat för hantering av Coronaviruset. News at www.vr.se Feb. 2020.
13. Wellcome Trust. Sharing research data and findings relevant to the novel coronavirus (COVID-19) outbreak. Press release 31 Jan. 2020 at https://wellcome.org/
14. Vetenskapsrådet. Samordning av öppen tillgång till forskningsdata. Statusrapport. ISBN 978-91-88943-33-0.

KLAUS VEDFELT / GETTY IMAGES

Tracing treatments on an ethical roadmap

The interventions offered in health and social services reflect what is considered to be a good life and how it should be promoted by society. Before introducing a new intervention – or phasing one out – policymakers must know how well it rhymes with set values and goals. This is why SBU highlights ethical aspects in many of its assessments.

EVERY MEASURE TAKEN in healthcare and social services has ethical significance. The aim is to do good and not harm. Measures should be based on the equal value and different needs of all people, where the greatest needs are given highest priority. The cost of interventions should be reasonably proportionate to the gains in health and quality of life that can be expected. The privacy and autonomy of individuals must be respected.

IN SITUATIONS WHERE it is difficult to achieve all goals equally well, and where some ethical principle will be more or less compromised whatever the decision is, an ethical dilemma arises. Different ethical values must be weighed against each other. The dilemma is made especially clear in regard to controversial issues such as euthanasia, genetic screening, genetic modification and late-term abortion. But even everyday decisions about diagnostic procedures, treatments and care can entail ethically significant trade-offs and limitations. Clarification ▶

► *Cont'd from page 13:*
of what is at stake, given various courses of action, is included in SBU's assessment of ethical aspects.

It is often important, even from an ethical standpoint, to analyse the economic consequences of various decisions. Expensive interventions that provide little benefit may displace others that are truly needed. Such impact is contrary to current legislation in Sweden and to the ethical platform that applies to such services.

MOREOVER, CERTAIN INTERVENTIONS are ethically questionable because they infringe upon the autonomy, independence and privacy of individuals and their families. The use of such methods among fragile and vulnerable people who may have difficulty expressing consent may pose highly significant ethical problems – even when intentions are good.

Therefore it is only natural that the SBU mission includes discussions of the ethical aspects of various interventions, as is reflected in the agency's comprehensive assessments, which serve as the basis for healthcare and social services decisions.

The purpose is not to determine which interventions should or should not be implemented. Instead, it is to analyse the potential impact of various interventions on values that are linked to the goals of the Swedish Health and Medical Services Act and Social Services Act. These laws concern good health and care on equal terms for the entire population, and a reasonable standard of living under good conditions.

HIGHLIGHTING ETHICAL ISSUES is particularly challenging when specific interventions and areas of use have been inadequately studied, such as completely new treatment options or new indications for old treatments. Scientific uncertainty regarding the benefits, risks and costs of the methods may complicate ethical reasoning. The potential impact of different decisions is difficult to predict.

Moreover, ethical consequences may vary among individuals, groups, situations, places and points in time. The impact is contextually dependent – for example, where, when, how and for whom a diagnostic method or treatment is intended. An intervention described by some as ethically uncontroversial may be considered unacceptable or highly questionable by others. Even in cases where everyone involved subscribes to the same fundamental values, individual attitudes towards specific interventions may diverge and even change over time.

Highlighting the ethical aspects of various interventions actually illuminates the values at stake, bringing to light ethical dilemmas, conflicting goals and differing perspectives, and allowing better-informed decisions to be made. Among important considerations are the effects of the interventions on:

- *equity and fairness:* Is there a risk that the intervention could entail inequitable and unfair access to healthcare resources?
- *autonomy:* Does the patient/user have the opportunity to understand and participate in decisions when the intervention is used? Does the intervention affect the person's potential to exercise self-determination in other situations?
- *privacy:* How does the intervention affect the physical and personal privacy of the individual and family members?
- *third party:* How are third parties (e.g. donors, close and biological relatives, surrogate parents) affected in terms of health equity, justice, autonomy, privacy, health and quality of life?

THE IMPACT ON the structure and funding of health and social services can also have ethical implications. Included here are issues regarding

- *cost effectiveness:* What is the balance between the cost of the intervention and the benefits to the patient?
- *resource allocation and organisation:* Are there restrictions that may affect who

gains access to the intervention, or that may overshadow other forms of care? Can the allocation of healthcare resources in the population be affected, and if so, who benefits or suffers? Is this in line with generally accepted guidelines for setting priorities, such that the allocation can be considered fair? Under current priority-setting rules, interventions that pertain to major healthcare needs are given priority over minor or insignificant needs.
- *regulatory:* Is the intervention of significance to something regulated by current laws?

INTERVENTIONS WITHIN healthcare and social services may also have an impact on values and interests. What is considered desirable may be influenced by what is pragmatically feasible. For example, new diagnostic and treatment methods may change our vision of what can be considered illness, which diagnoses to look for and what should be treated. Consequently, there is reason to describe how an intervention relates to

- *professional values:* Do the values found within relevant healthcare professions influence use of the intervention in such a way as to lead to unequal access? What is the effect on freedom of action and the potential for healthcare providers to fulfil their professional roles in accordance with current professional ethics? Does the method impact professional identity?
- *social norms:* Is the method compatible with different beliefs – does it conflict with religious, political or cultural convictions?
- *special interests:* Do special interests have an influence on use of the intervention that may result in unequal access? Do researchers, policymakers, innovators, or manufacturers have a vested interest in use of the method or its evaluation?

SBU'S ASSESSMENTS of the scientific literature highlight both existing knowledge and evidence gaps. Research ethics issues may be of relevance in

- *continued research:* When there is no scientific basis to underpin the efficacy of the intervention, do ethical and/or methodological problems arise when conducting studies?
- *prior research:* Are there indications that the studies on which the assessment is based were conducted in a way that entails research ethics issues?

Finally, various long-term ethical implications need to be discussed, such as the impact on societal structure and culture. For example, use of a particular method may lead to new moral imperatives. When a screening programme is introduced to discover a particular disease, many of those who are diagnosed will also expect effective therapy. Such a situation may alter how society views the disease, indications for treatment, the responsibility of the individual and the healthcare system, as well as the doctor-patient relationship. Is patient self-esteem or standing and reputation in society impacted?

Assessing the ethical aspects of medical and social methods entails a description of the balance between probable ethical benefits and the risk of ethical disadvantages. Such issues are of relevance to most people, including their ramifications for autonomy, privacy and dignity. Ultimately, it becomes a question of the impact on human rights. ◆ **RL**

References

Heintz E, et al. Framework for systematic identification of ethical aspects of healthcare technologies: the SBU approach. Int J Technol Assess Health Care 2015;31:124-30.

Hofmann B. Towards a procedure for integrating moral issues in HTA. Int J Technol Assess Health Care 2005;21:312-8.

SBU. Kapitel 13. Etiska aspekter. I: Utvärdering av metoder i hälso- och sjukvården och insatser i socialtjänsten: en metodbok. Stockholm: SBU, 2020. Downloaded 2021-09-14. Available at www.sbu.se/metodbok.

KLAUS VEDFELT / GETTY IMAGES

ONGOING

Some Current SBU Projects

CAESAREAN SECTION ON MATERNAL REQUEST
Sigurd.Vitols@sbu.se
Publication: winter 2021/22

COMPLEX INTERVENTIONS FOR CHRONIC PAIN
Anna.Christensson@sbu.se
Publication: winter 2021/22

CONTINUITY OF CARE
Per.Lytsy@sbu.se
Publication: summer 2021

COVID-19: LONG-TERM SYMPTOMS
Elizabeth.Ahsberg@sbu.se
Updated continuously

DIABETES & DIETARY TREATMENTS
Goran.Bertilsson@sbu.se
Publication: spring 2022

FEAR OF CHILDBIRTH, ANXIETY & DEPRESSION DURING PREGNANCY
Nathalie.Peira@sbu.se
Publication: spring 2021

FIBROMYALGIA
Anna.Christensson@sbu.se
Publication: winter 2021/22

LIPEDEMA
Helena.Domeij@sbu.se
Publication: autumn 2021

MOBILITY AIDS FOR PHYSICAL DISABILITY
Susanna.Larsson.Tholen@sbu.se Publ: autumn 2021

PERINEAL TEARS DURING CHILDBIRTH
Naama.Kenan.Moden@sbu.se Publ: spring 2021

RETURN TO WORK AFTER LONG-TERM SICK LEAVE
Elizabeth.Ahsberg@sbu.se
Publication: spring 2022

SUICIDE PREVENTION PROGRAMS FOR YOUTH
Agneta.Pettersson@sbu.se
Publication: autumn 2021

VULVAR VESTIBULITIS
Karin.Wilbe.Ramsay@sbu.se
Publication: summer 2021

MEDICAL AND SOCIAL
Science & Practice

EXECUTIVE EDITOR Ragnar Levi, ragnar.levi@sbu.se • PUBLISHER Susanna Axelsson • TEXT Ragnar Levi [RL]
MAILING ADDRESS PO Box 6183, SE-102 33 Stockholm, Sweden • PHONE +46-8-412 32 00 • www.sbu.se
EMAIL registrator@sbu.se • TWITTER @SBU_en • DESIGN Alenäs Grafisk Form
TRANSLATION Susan & Charles Larsson • CIRCULATION (SWE) 145 000 • ISSN 1104-1250

VICTORIA SHAPIRO / SHUTTERSTOCK