Assessment of Positive Contributions to Health of Publicly Traded Companies related to Medical Devices

Department of Environmental Health
Harvard T.H. Chan School of Public Health

Overview

This document describes in detail a rational, objective, and scalable methodology to assess the positive contributions to health effects offered by publicly traded companies related to medical devices.

Assessment of companies that manufacture and commercialize medical devices

Benefits for medical device companies are estimated by getting the list of medical devices related to the top 20 causes of mortality and 20 top causes of disability (Table 1) for each medical device company. A medical device is an item that is used as an auxiliary instrument to provide proper care either by measuring health metrics, assisting in delivering drugs or medical therapies without having a pharmacological or therapeutical effect themselves, or by providing a therapeutic action on their own (like brackets, orthopedic instruments, ultrasound diagnostic medical devices, pacemakers or dialysis machines).

Table 1. Top 20 worldwide causes of mortality and disability in 2020 (World Health Organization)

Top 20 worldwide causes of mortality (2020)	**Top 20 worldwide causes of disability (2020)**
Ischemic Heart Disease (IHD)	Low back pain
Stroke	Major depression disorder
Chronic Obstructive Pulmonary Disease (COPD)	Musculoskeletal disorders
Lower Respiratory Infections	Neck pain
Neonatal Conditions	Migraine and anxiety disorders
Tracheal, Bronchial and Lung Cancer	Chronic Obstructive Pulmonary Disease (COPD)
Alzheimer's and other dementias	Influenza and upper respiratory infections
Diarrhea and gastrointestinal diseases	Drug use disorders
Diabetes	Diabetes
Chronic Kidney Disease	Osteoarthritis
HIV/AIDS	Asthma
Colorectal Cancer	Lower Respiratory Infections
Tuberculosis	Alzheimer's and other dementias
Hypersensitive Heart Disease	Stroke
Stomach Cancer	Ischemic Heart Disease (IHD)
Other cancers (small cell cancer, multiple myeloma, leukemia, etc.)	Cancer of any kind
Neonatal encephalopathy	Diarrhea and gastrointestinal diseases
Malaria, Zika, Dengue Fever, and other infectious diseases transmitted by mosquitoes	Chronic Kidney Disease
Congenital diseases	Parkinson's disease
Maternal mortality	Malaria, Zika, Dengue Fever, and other infectious diseases transmitted by mosquitoes

Once these medical devices are listed per company, then we divide medical devices into the following categories:

- **Class I devices are subject only to general controls.** They typically present the lowest potential for harm and are simpler in design than Class II or Class III devices. Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

- **Class II devices are those for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness.** In addition to complying with general controls, Class II devices are also subject to special controls identified by the agency, including special labeling requirements, performance standards, and post-market surveillance. Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.
- **Class III devices generally are those for which insufficient information exists to determine that general or special controls are sufficient to provide a reasonable assurance of safety and effectiveness**. Class III devices include replacement heart valves, pacemakers, silicone gel-filled breast implants, and implanted cerebellar stimulators.

An excellent tool to assist in classifying medical devices is the database for medical devices analyzed and approved for use in the United States of America prepared by the U.S. Food and Drug Administration available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm

After classifying medical instruments for every company using these three categories, the research group assigns a medical effectiveness value for each device which is usually listed in a percentage of the patients treated with the medical device that achieve a particular health outcome, compared to a placebo in monotherapy in a cohort study[1].
The preferred way to determine the medical effectiveness of medical devices is by reviewing peer-reviewed journal articles and clinical effectiveness studies for therapies related to the medical devices under analysis. However, one of the biggest challenges in this methodology is that there is almost no objective and official information for clinical effectiveness for Class I and Class II medical devices. Additionally, this information is scarce for Class III devices. Peer-review research articles state the clinical efficacy of pacemakers, heart valves, and dialysis machines because they are directly related to preserving human life. Still, there are no studies

[1]. We assume that differences in genotypes in human populations worldwide are not as drastic as significantly changing a drug's effectiveness.

or official reports on the overall medical effectiveness or influence of bandages, surgical instruments, and devices like glucometers in treating specific health outcomes. When information from peer-reviewed scientific articles is not available, a medical panel could be assembled to offer an expert opinion about the effectiveness of different medical therapies. These initial effectiveness values should always be considered as preliminary. According to the Quality of Information Scorecard Protocols described in **Appendix I**, they should be penalized when analyzing uncertainty.

There is no clinical effectiveness information for the most usual combinations of medical devices and drugs, only the effectiveness of monotherapy. Therefore, only monotherapy effectiveness with its corresponding confidence intervals is used to estimate health benefits to have an objective measure of the benefits of every specific medical device.

Information about average mortality, hospitalizations, and sick days among people with a particular health outcome related to each medical device is collected to create models to estimate benefits. Then the number of patients under treatment by each medical device is calculated by getting the overall number of medical devices sold worldwide or at least in the most critical major markets (the United States, the European Union, China, India, Japan, Indonesia, Russia, Brazil, Pakistan, Nigeria, and Mexico). An alternative method is to use revenues and baseline prices for medical devices to estimate the number of medical devices sold every year in the major markets of interest. Health benefits will be assessed on an annual basis because they are the only ones tied directly to the revenues for that year. Then, we will define a primary number of uses for each medical device based on the number of recommended users or overall service life for the device. In this way, we can determine the number of patients served every year by a medical device. For example, a band-aid or dialysis filter will only be used once, and a glucometer is likely to be used 1,500 times during the product's lifetime with an average of one use per day.

A medical device might be used for more than one health outcome. Therefore, the average percentage of use per medical device for each health outcome should come from medical

practitioners in every country to estimate the number of users served for every medical outcome.

Suppose worldwide information about the number of medical devices sold is not available. In that case, we use financial reports from each company to determine the percentage of revenues per medical device family per country. We then use information about the rate of revenues related to each kind of medical device and the average price for the medical device in the USA to estimate the number of likely patients under treatment in other markets. A simple way is to multiply the price for a particular medical device in the USA by a purchase parity index for every country or significant market. This will give us an equivalent willingness-to-pay price for a specific market with confidence intervals. This procedure compensates for the lack of price negotiations for the U.S. health sector. Due to local legislation, some medical devices are available in certain countries at a lower price.

The process requires information about treatment effectiveness once a diagnosis occurs. Additionally, we get the prevalence and epidemiology for each medical outcome diagnosed by the medical device.

The basic process to estimate mortality, hospitalizations, and sick days prevented by the company uses all of the information described above to have objective results about the impacts of healthcare products by company (Figure 1; Figure 2).

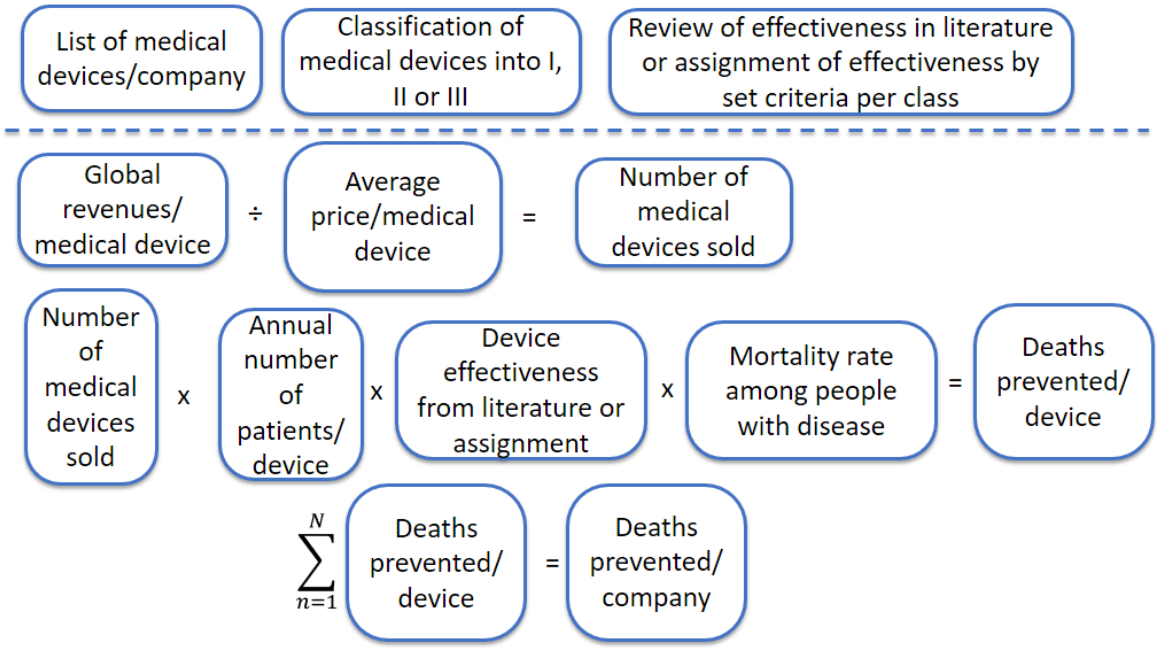


Figure 1. Basic process to estimate annual mortality prevented by a medical device company

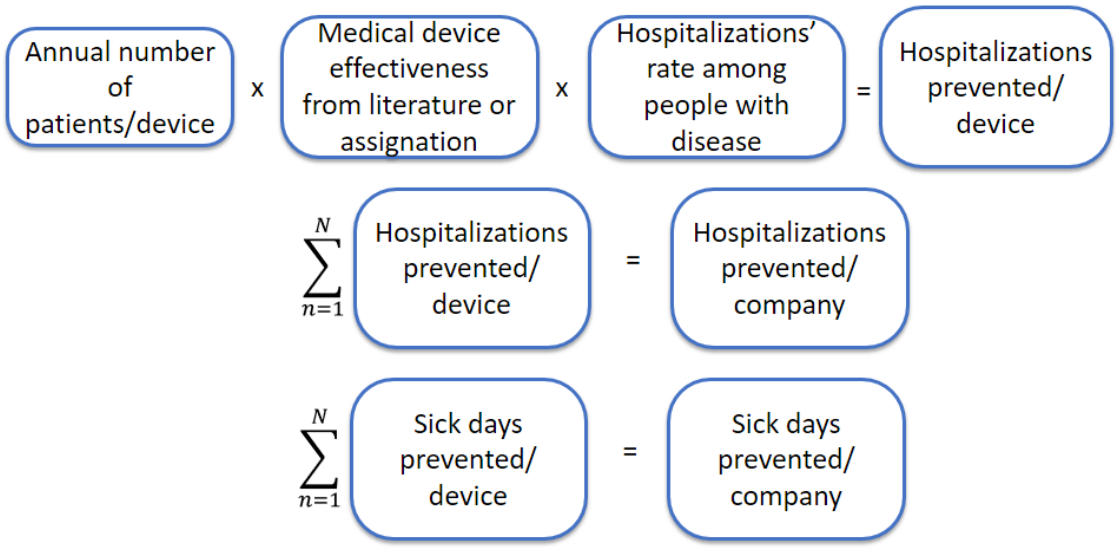


Figure 2. Basic process to estimate annual sick days prevented by a medical device company

An uncertainty and sensitivity analysis for the benefits of each device is performed using a quality of information scorecard for health information that was developed to identify and characterize uncertainty for each piece of information in the model. This is used to create statistical distributions with variation in a Monte Carlo Analysis; each company's aggregate

mean health benefits are reported, and a healthcare ranking for overall global benefits of companies is prepared (in descending order of benefits).

An important assumption is that all healthcare benefits have a functional baseline (they are not time-dependent) because people are either doing the therapy to reach a particular health goal or not. Adverse health outcomes manifest due to a lack of proper medical treatment.

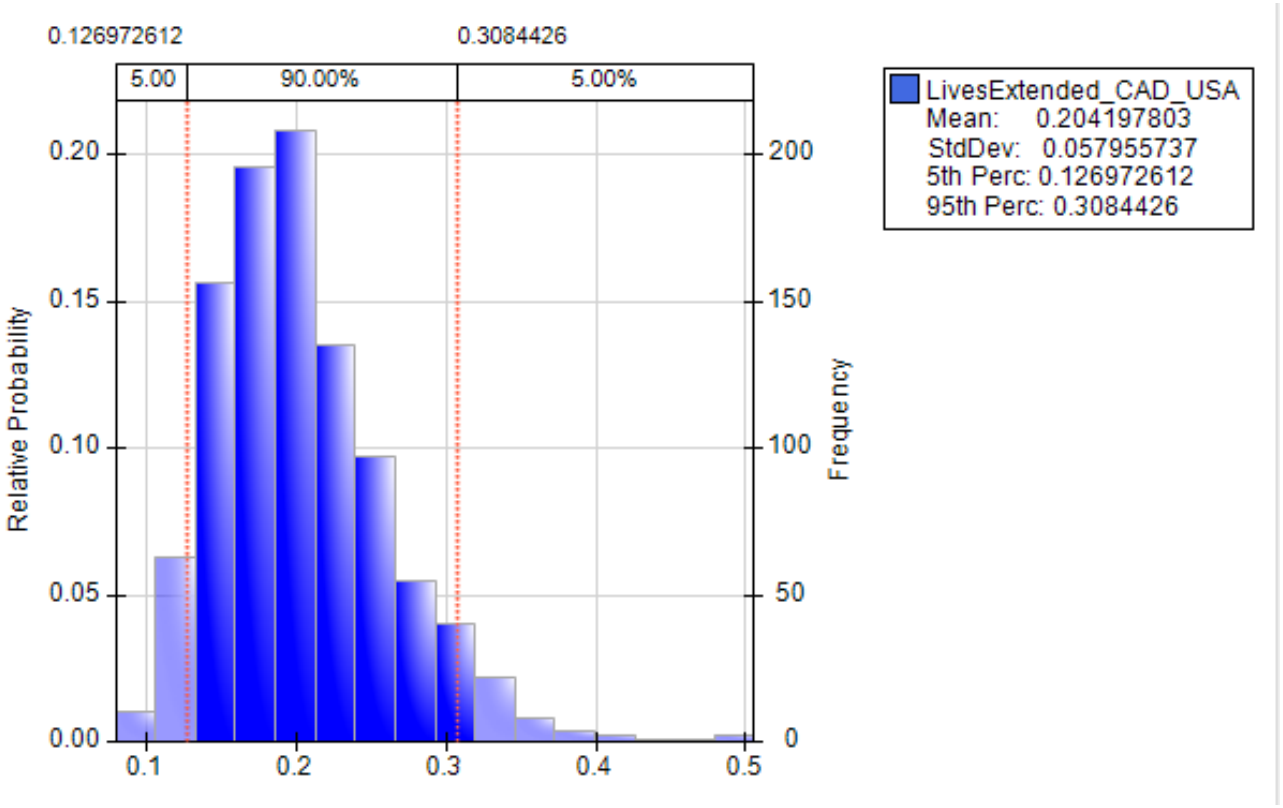
Example of using this methodology for ultrasound medical devices applied to coronary artery disease (CAD) in the United States.

Coronary artery disease (CAD) is an ischemic heart disease that killed approximately 365,914 individuals out of 18.2 million people with the disease in the USA in 2019. (CDC, 2019; WHO, 2020). A way to reduce CAD mortality is by detecting this disease in its early stages. This diagnosis might lead to changes in the patient's diet, cardiovascular management therapies, or a surgical procedure to bypass obstructed coronary arteries.

CAD diagnosis by itself is likely to reduce mortality by 29% compared to undiagnosed people (95% Confidence Interval (CI) between 23.5% and 35.3%). This measure of effectiveness comes from polling cardiologists and medical experts in hospitals in Boston in the United States (Sanchez-Pina, 2021). This mortality reduction effectiveness is used temporarily while scientists estimate a more solid value based on a comprehensive assessment of effectiveness from medical studies or a wider consultation of the international medical community.

Usage rate for ultrasound medical devices used for cardiovascular diseases comes from field clinics and information from the manufacturer of the ultrasound medical devices. As an example, if we assume that there are five ultrasound procedures for CAD per day and we consider that we need two procedures to make a proper diagnosis and that the clinic or hospital works for 260 days/year, then we have a total of 650 cardiovascular diagnosis/device/year. Considering effectiveness of 97% for diagnosing CAD, then the potential mortality prevention benefits are:

Deaths prevented by elective diagnostic ultrasounds per device in the USA= 0.29*650 procedures/year*0.975*(365,914 CAD deaths/year in the USA/330 million people in the USA) = 0.202 deaths prevented/year/medical device (90% CI [0.127, 0.308]).



Appendix I

Generation of mean values and uncertainty factors used in Monte Carlo Analysis for energy efficiency, renewable energies, and healthcare products

Estimation of averages and coefficients of variation for output parameters in every step of processes under analysis

A common practice for scientific estimations and field data is to report mean values for input and output parameters. Most of the time, a measure of dispersion is reported for the mean values to include uncertainty. There are several components of uncertainty in scientific or technical analysis; some of them are:

-**Variability and stochastic error:** The values describing inputs and outputs due to measurement uncertainties, process-specific variations, temporal variations, etc.

-Appropriateness of the input or output flows: An input or output might not perfectly match the input or output observed in reality due to temporal or spatial approximations (example: Dialysis therapies performed in Mexico in 2015 might be different from dialysis therapies performed in Mexico in 2020).

-**Model uncertainty:** The model used to describe the process may be inappropriate (using a linear instead of a non-linear relationship in modeling).

-**Neglecting essential processes in the model:** Not all relevant information might be available to describe the process entirely. These unknown inputs and outputs are missing in the scientific or technical analysis.

A method to improve data quality was used to estimate uncertainties in a technical life cycle analysis by Pedersen Weidema and Wesnaes in 1996. This method proposes a matrix of data quality indicators and corresponding coefficients of variation; in this way, the essential

uncertainty of a parameter can be adjusted to reflect other sources of variation. The overall coefficient of variation is estimated by calculating the square root of the sum of the squares of the individual coefficients for each uncertainty source.

$$(1+ Cv) = \exp [\sqrt{([(\ln(U_1)]^2 + [(\ln(U_2)]^2 + [(\ln(U_3)]^2 + [(\ln(U_4)]^2 + [(\ln(U_5)]^2 + [(\ln(U_6)]^2 + [(\ln(U_b)]^2)}]$$

Where:

Cv: Coefficient of Variation

U_1: Uncertainty Factor of Reliability

U_2: Uncertainty Factor of Completeness

U_3: Uncertainty Factor of Temporal Correlation

U_4: Uncertainty Factor of Geographic Correlation

U_5: Uncertainty Factor of Technological Correlation

U_6: Uncertainty Factor of Sample Size

U_b: Basic Uncertainty Factor

Uncertainty factors are determined by applying a matrix of data quality indicators and a table of default uncertainty factors. The matrix of data quality indicators describes qualitative characteristics for each one of the categories of uncertainty factors; descriptions are used to assign an indicator score of uncertainty. Values for uncertainty factors are determined by matching the indicator score of uncertainty from the data quality matrix with its corresponding type of uncertainty in the table of default uncertainty factors. A more prominent primary uncertainty factor is applied when there is missing information in the data quality matrix.

Overall uncertainty estimations are given in a unit process level (for example: tons CO_2eq/KWh, Price per annual cost of therapy, etc.) The matrix of data quality and default uncertainty factors are shown in tables 3 and 4.

Table 3. Pedigree Matrix used to assess the quality of data sources for medical device/ healthcare companies derived from (Pedersen Weidema & Wesnaes, 1996)

Level	1	2	3	4	5	Notes
Reliability	Verified data based on measurements or approved human clinical studies	Verified data based on assumptions OR non-verified data based on measurements or animal studies	Non-verified data partly based on qualified estimates	Qualified estimate (i.e., by health expert) Data derived from theoretical information (molecular models, genetic theory, etc.)	Non-qualified estimate	Verified means published in companies' public environmental or health reports, official statistics, etc. Unverified means: personal information by letter, fax, or e-mail
Completeness	Representative data for diverse human subjects over an adequate period to even out normal fluctuations.	Representative data from > 50 % of potential patient genotypes to even out normal fluctuations over an adequate period.	Representative data from only some individuals (<<50 %) relevant to health outcome considered OR > 50 % of individuals but for shorter periods	Representative data from only one individual relevant for the health outcome considered for a long time OR some individuals but from shorter periods	Representativeness unknown or data from one individual AND from shorter periods	Length of adequate periods depends on process/ technology/ health outcome
Temporal Correlation	Less than three years of difference to our reference year	Less than six years of difference to our reference year	Less than ten years of difference to our reference year	Less than 15 years of difference to our reference year	Age of data unknown or more than 15 years of difference to our reference year	The score for processes with investment cycles of less than ten years; for other cases, scoring adjustments can be made accordingly
Geographical Correlation	Data from the country or area under study	Average data from a larger area in which the area under study is included (for example, information for all of Europe if we are analyzing only Dutch patients)	Data from a smaller area than the area under study or environmentally similar regions (for example, a province or state instead of the whole country)	Data from a distinctly different area of the world (Northern Europe instead of South Western Australia, for example)	Data from an unknown origin in the world	The similarity is expressed in terms of environmental or health legislation. Suggestion for grouping: - North America, Australia; - European Union, Japan, South Africa; -South America, North and Central Africa, and the Middle East; Russia, China, Far East Asia

Health or Biological Correlation	Data from medical device companies or government labs related to clinical studies for the same therapy and identical health outcomes	Data from medical device companies or government labs related to clinical studies for similar drugs or molecules for identical health outcomes	Data from medical device companies or government labs related to clinical studies for similar drugs or molecules for similar health outcomes	Data from medical device companies or government labs related to lab studies for similar drugs or therapies for the same health outcomes	Data from medical device companies or government labs related to lab studies for similar drugs or therapies for the similar health outcomes	Examples of different health outcomes: - Cardiovascular Disease and Parkinson's Disease Examples of similar health outcomes: Myocardial arrest and Stroke Examples of similar drugs: aspirin and aspirin enriched with caffeine. Natural Insulin and artificial cell openers for glucose
Sample Size	>100	>20	>10	≥ 3	Unknown	Sample size behind a figure reported in the information source.

Table 4. Default uncertainty factors applied together with a matrix of data quality indicators

Indicator Score	1	2	3	4	5
Reliability	1.00	1.05	1.10	1.20	1.50
Completeness	1.00	1.02	1.05	1.10	1.20
Temporal Correlation	1.00	1.03	1.10	1.20	1.50
Geographical Correlation	1.00	1.01	1.02	1.05	1.10
Further Technological correlation	1.00	1.10	1.20	1.50	2.00
Sample size	1.00	1.02	1.05	1.10	1.20

The value (1 + Cv) is equal to the square of the geometric standard deviation (σ_g^2) for the lognormal distribution. This is important because several reports in the field of risk assessment and impact pathway analysis have shown that the lognormal distribution seems to be a more realistic approximation for the variability in fate and effect factors than the normal distribution (Hofstetter, 1998). Because emission measurements may not show negative values, the lognormal distribution is also applied to life-cycle inventory data. The lognormal distribution is assumed by default to all process steps in food production unless reliable field data indicates otherwise. Suppose actual field measurements or reliable and verified data suggest that a parameter has a normal distribution. In that case, the coefficient of variation is determined by dividing the sample standard deviation by the sample mean.