Costs and environmental sustainability of Dried Blood Spot versus Whole Blood sampling for patients receiving immunosuppressive therapy after kidney transplantation

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1 Introduction

In the last decade, one of the big challenges regarding healthcare is the rise of healthcare costs. In the Netherlands alone, total healthcare costs increased by 16% between 2016 and 2020 [1]. The expenses for 2022 are estimated at €93 billion, which is more than 25% of the total state budget [2] [3] [4]. Without policy adaptations, healthcare costs are expected to rise with 2 to 3 percent each year until 2060 [5] [6], meaning drastic changes need to be made to keep healthcare affordable. Important reasons for the vast increase are the ageing and growing population, comorbidities, a higher prevalence of chronic diseases and more expensive treatment [7] [8] [9].

Besides this focus on increasing costs, more awareness for environmental sustainability in healthcare can be seen as well. The fact that humans play an important role in environmental damage, especially climate change, is broadly known and extensively dealt with in literature [10] [11] [12] [13]. Despite the fact that research into the sustainability of healthcare has been limited up until recently, it is clear that the environmental impact of the sector is significant. With carbon emissions of 11 megaton, it is responsible for 7% of the national footprint in The Netherlands [3]. A similar percentage was found for Australia [14], and in the USA this was 10% [15]. Reducing this footprint would not only be of value to tackle climate change. The population will benefit directly as well, as climate change has shown to affect our health. This is due to more extreme weather, such as droughts and floods, air pollution and an increase in disease carriers like mosquitoes and ticks [16] [17] [18].

Based on the above, it is clear that costs and sustainability are important topics to consider, especially if we want to ensure equally good or better healthcare for future generations. Evaluating healthcare technologies on financial and environmental impact should therefore be common practice in any hospital or country. Health economics is the field that focuses on effectiveness, efficiency and value in healthcare [19]. There is a strong fundamental basis of methodologies, guidelines and literature on ideas like value based healthcare or cost-effectiveness analysis [20] [21] [22] [23] that makes evaluating costs more practical. Besides that, research into the sustainability of the healthcare sector is gaining popularity. Such research is executed for example through life cycle thinking and/or analyses [24] [25] [26] [27].

Lowering energy consumption is one example of how a reduction of costs and an increase in sustainability can go hand in hand [28]. Assessing technologies and practices in healthcare on both costs and sustainability may therefore help in faster implementation of best practices or highlight areas for improvement. However, only limited literature exists on assessing environmental impacts and costs of healthcare practices or products within one study [29] [30].

In this study, the financial and environmental impact of an innovative method for monitoring patients after kidney transplantation will be assessed. This novel method requires some adjustments in the care pathway and is used in a few hospitals only, including the LUMC. In the LUMC alone, more than a thousand patients are subject to this type of monitoring, year after year. Clinical effectiveness for both methods is discussed in previous literature [31] [32] [33] and show that both methods are equally suitable for this type of monitoring. However, no extensive comparison of costs and/or environmental impact between both methods has been carried out yet. Regarding the adjustments in the care pathway and the amount of patients subject to this type of monitoring, evaluating both

alternatives may be beneficial for healthcare expenditure and/or the environment. The study is relevant especially for the LUMC, judging from its' ambitions on savings in the financial budget and reductions of the environmental impact [34] [35]. Other hospitals might benefit as well, as they can adapt or maintain their own process, depending on the outcome. Main outcomes of the study are total costs, carbon footprint and biggest contributing factors in these aspects for the two therapeutic drug monitoring methods.

In the following section (2), the medical context of kidney transplantation and both sampling techniques are discussed. Theory behind the cost and environmental analysis are introduced in sections 3.1 and 3.2 respectively. Methods and results are discussed in sections 4 and 5, and finally the discussion in section 6.

2 Therapeutic Drug Monitoring

In the Netherlands, about 2000 patients are diagnosed with renal failure annually, meaning their renal function is 15% or less compared to normal [36]. For these patients, kidney transplantation is often the best option, which is done around 1000 times a year. After undergoing a kidney transplantation, patients take immunosuppressive medication to prevent the graft from being rejected [32]. The use and improvements of these immunosuppressants have improved graft survival [37], but dosage of these drugs must be closely monitored as the pharmacokinetics among patients is highly variable. A mismatch in dosage can result in graft rejection when too low or in drug toxicity when too high. Therefore, blood tests are performed frequently to understand the patterns of the drug absorption by the body and to tune dosing. This testing and tuning is known as Therapeutic Drug Monitoring (TDM) [32].

The LUMC is one of the seven medical centres where kidney transplantation is performed [38], which means TDM is provided for people from all over the country in this hospital. For each patient, two types of examinations are done:

- Measurement of trough levels. This means the patient's blood is collected just before medication intake. These measurements are done multiple times each year and can be carried out by the local hospital (i.e. not the LUMC when the patient is under treatment elsewhere).
- Measurement of Area Under the Curve (AUC) levels. For AUCs, multiple blood samples are taken to investigate the medication uptake over a longer time period. For example, blood can be drawn just before, 2 hours, 3 hours and 4 hours after medication intake, but these intervals can differ by medication type. An AUC is done three times within the first year after transplantation and only carried out by the LUMC. After the first year, AUCs are done annually, in the same period as the yearly check-up. The 'schedule' for each type of examination can be found in Table 1.

Table 1: Trough and AUC examination times

WEEK	YEAR 1	YEAR >1
2	trough	-
3	trough	-
4	trough	-
6	AUC	-
8	trough	-
10	trough	-
12	trough	-
16	trough	trough
20	trough	-
24	AUC	-
30	trough	-
36	trough	trough
44	trough	-
52	AUC	AUC

AUC: Area Under the Curve analysis

As mentioned before, TDM can be executed in two ways, which has implications for the various stages in the process. These stages and differences will be discussed in sections 2.1 - 2.4. The biggest difference lies in the manner of how blood is sampled (blood acquisition stage) and all the other stages will be referred to on that basis:

- Whole Blood (WB) sampling is the current standard to collect blood for analysis and diagnosis and is also called phlebotomy. This involves the puncture of a vein in an arm to let blood out of the circulatory system. Per sample, 2-4 mL blood is collected in special tubes [39] [40].
- Dried Blood Spot (DBS) sampling is an alternative where blood is acquired via a finger prick using an (automated) lancet and collected on a filter card [41] [31]. On this card, the blood spreads to form a spot. The punctured finger is either directly pressed against the filter card or against a small capillary. This capillary is part of a sampling device (the DBS kit) and collects the blood to transfer it to the card. The latter method is called *volumetric* DBS sampling, as the capillary allows only a specific volume of blood (10 μL) to be transferred to the filter card (see figure 1). This volumetric sampling overcomes certain issues regarding the analysis which makes it more reliable than direct DBS collection [32]. For this reason, volumetric sampling is used in the LUMC. After sampling, the blood is dried for 24 hours before it is analyzed.

In total, four stages for TDM are identified. These are described below and schematically presented in figure 2.

2.1 Doctor's appointment

As shown in table 1, AUCs are performed multiple times in the first year and yearly after that. An AUC is planned in the same period as physical appointments with the physician. Such appointments serve as check-up on how the patient and the graft are doing. For WB, the AUC is planned on the same day, for DBS a few weeks before the doctor's appointment.

Figure 1: Volumetric DBS kit

2.2 Blood sampling

Depending on the medication schedule, three or more samples are drawn for the AUC and each sample is drawn for at least 30 minutes apart. For the first sample (trough sample), the patient should not have taken his/her medication for that day yet. Directly after the first sample is taken, medication is taken and the time until the next sample starts.

As mentioned before, the blood sampling stage is where the main differences lie between WB and DBS.

For WB sampling, it involves the patient going to the phlebotomy department and having his or her blood drawn by the phlebotomy technician for several times. For the first sample, the patient waits with his or her registration number until being called in by the phlebotomist. The phlebotomist checks the references and whether the patient has not taken his/her medication yet. After the first sample is taken, the patient takes the medication under supervision of the phlebotomist and receives a time schedule for when the other samples must be drawn. Then the patient leaves the phlebotomy department and waits for the next time slot. The time between two samples is sometimes filled with other appointments but can be 'free time' as well.

For DBS sampling, the patient receives two DBS kits, a set of safety lancets, instructions, and a form during the previous appointment or by mail. Before each sample, the patient washes his or her hands to make sure the blood is not contaminated. For each sample, a new safety lancet is used to prick the finger. On the form, the patient writes down at what times the sampling is executed, the type and dosing of medication. After the blood samples are collected and have dried for 24 hours, the kit is put in a sealed bag in an envelope and sent back to the hospital via regular mail delivery.

2.3 Analysis

When the collected blood has arrived at the lab, the samples are processed in batches by an analyst. This involves adding various chemicals and reagents to make sure the analysis device can process the sample. The resources, chemicals and reagents used and steps to be undertaken are comparable for WB and DBS but differ mainly in the amounts used. One factor that makes a difference is the type of medication. Five types of medication require TDM, namely Tacrolimus (TAC), Everolimus (EVER), Ciclosporine

(CIC), Mycophenolic Acid (MPA) and Sirolimus. Sirolimus is excluded from this research as AUC's are hardly ever determined for this type. For tacrolimus, different brands are available, which has implications for the AUC times, as shown in table 2. All medication types can be prescribed separately, but a combination between MPA and any of the other is possible as well. For DBS, all medication types can be analysed simultaneously in one sample. For WB, MPA must be analysed in serum, while for TAC, EVER and CIC whole blood suffices. Therefore, MPA is always analysed separately. This is important, as this has implications for the number of analyses.

Table 2: AUC times per medication

Hour	TAC - adv	TAC - env	TAC - pro	EVER	CIC	MPA
0	1	1	1	1	1	1
0.5	-	-	-	-	-	1
1	-	-	-	1	-	1
2	1	-	1	1	1	1
3	1	-	1	1	1	1
4	-	1	-	-	-	-
8	-	1	-	-	-	-
12	-	1	-	-	-	-

adv (Advagraf®), env (Envarsus®) and pro (Prograft®) are Tacrolimus brands
TAC: Tacrolimus, EVER: Everolimus, CIC: Ciclosporin

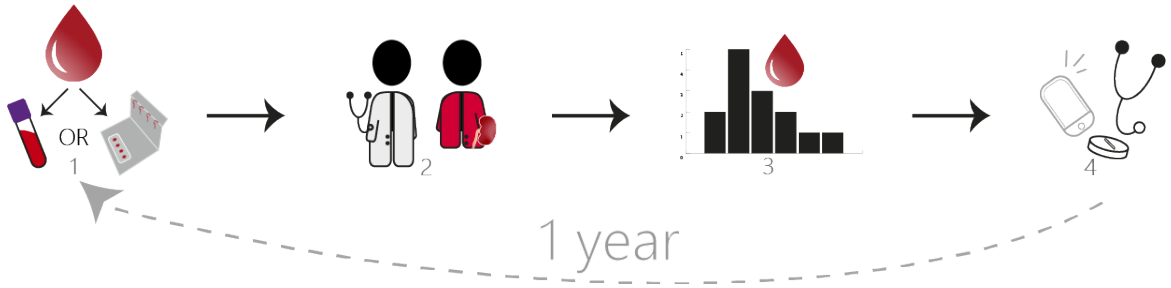
After processing the samples, they are put into a *Liquid Chromatography - Tandem Mass Spectrometry* (LC-MS/MS) device, which measures the medication concentration with high accuracy. The settings of this device differ for WB and DBS analyses, as the chemical and reagent concentrations are different after the sample preparation.

When the LC-MS/MS analysis is complete, the results are automatically incorporated in the laboratory information system (GLIMS). The analyst checks whether results seem plausible and marks the analysis as completed.

2.4 Feedback

A hospital pharmacist assesses the results of the analysis and calculates the AUC of all samples for one patient. The AUC, together with a dosage advice, is then entered into the hospital information system (HiX), where the physician assistant or nephrologist can find the result. He or she then discusses this result with the patient. For WB, this is done via phone, as the results are not available yet during the physical appointment. For DBS, the results are discussed during the physical appointment. This is possible because the patient sent the DBS-kit to the hospital some time earlier.

Figure 2: Schematic overview of the care pathway of TDM



1: Blood is sampled through phlebotomy (WB) or with a DBS kit. 2: The patient and doctor have an appointment to evaluate how the patient is doing. This appointment is scheduled between two sample drawings for WB. 3: Blood samples are analysed in the hospital lab. The hospital pharmacists calculates the AUC and gives a dosage advice. 4: The doctor discusses the result with the patient. This a separate appointment by phone for WB. For DBS, the results are discussed during the doctor's appointment (step 2) if the results are available.

3 Theoretical background

3.1 Cost analysis

Costs associated with DBS were investigated by two studies [42] [43], although one of them had DBS additional to WB rather than as a substitute, while the other was a case study of two children. More evidence on the economical implications of DBS is thus desired. This could be especially insightful since quite some alterations in the care pathway occur compared with WB sampling. These alterations might have notable consequences in the costs.

As mentioned before, different types of economic analyses are available. Such analyses are used to compare at least two available options. One is the baseline or comparator arm, and the other the intervention arm. Examples are cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA) [44]. All these analyses quantify total costs, but differ in the type of units used for the outcome measurement. For example, cost-minimisation is used to evaluate options that are assumed to have the same effect. The least expensive option is considered the best. Effectiveness is presented in a natural unit, such as successful treatments, while in a cost-benefit analysis both costs and outcomes are expressed in monetary terms.

3.2 Environmental analysis

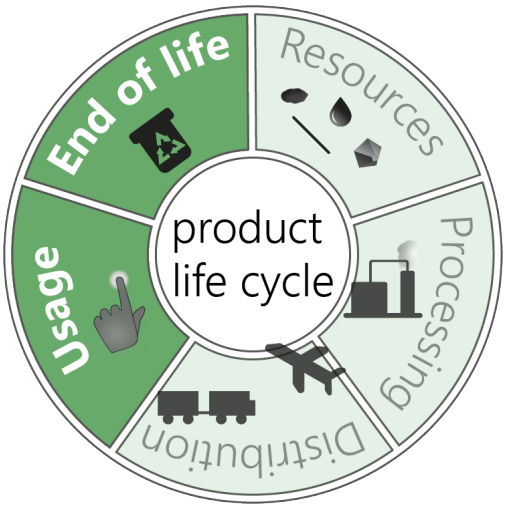
Environmental impacts are assessed through a Life Cycle Analysis (LCA), for which international guidelines are developed by the International Organisation for Standardisation (IOS). It is a methodology (ISO number 14040) to quantify the environmental impact of the 'life cycle' of a service, product or process [45]. LCA's for various healthcare processes and products have been carried out increasingly [27] [46] [26]. Comparisons of environmental impacts in a healthcare setting were done for example on disposable versus reusable products [47] [48][49], gynecology [50] [25], and procedures between countries [24], but as far as we know, this is the first study on the sustainability of different blood sampling methods and analysis techniques.

A full product's life cycle consists of five phases (figure 3):

1. Obtainment of raw materials;
2. Manufacturing & Processing;
3. Transport;
4. Usage;and
5. End of life (waste) treatment.

When all phases are included in the analysis, this is known as the 'Cradle to grave' model. In many LCAs however, only some phases are included to avoid overcomplex analyses that become too difficult to carry out or understand.

Figure 3: Five phases of a life cycle



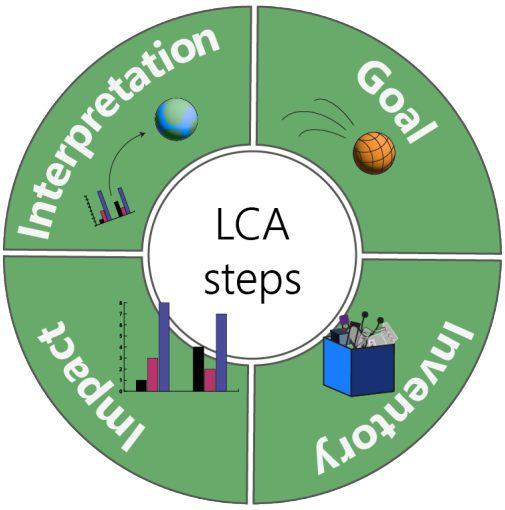
Resource: all activities concerning the obtainment of raw materials; Processing: all activities, raw materials and/or intermediate products needed for the production of product x; Distribution: transportation to the desired location; Usage; all activities associated with using the product; End of life: the reuse, disposal or recycling of a product. Darker green phases are included in this study

An LCA consists of four steps:

1. Defining the goal;
2. Creating an inventory;
3. Assess the impact; and
4. Interpreting the results.

Figure 4 presents a schematic view of the different steps of an LCA.

Figure 4: Steps of a life cycle assessment



Goal: what is the functional unit? Which impact categories are taken into account?; Inventory: Collect and list all resources used and by which amounts; Impact: calculate results for included impact categories; Interpretation: What do these results mean on a short-term and a long-term. How does this affect the world on a broader scale?

3.2.1 Goal

In this phase, it is decided what the functional unit will be. The functional unit represents the product, activity or service that will be assessed on environmental impact. The functional unit should represent a realistic scenario or be a value encountered in daily life. Examples of a functional unit could be:

- Drinking 100 cups of coffee with a mug or disposable paper cups;
- Driving from Leiden to Enschede by train or by car;
- Make a diagnosis based on lab tests or a CT scan;
- Doing surgery using sevoflurane, propofol or desflurane as anesthetic.

It is also important to define what will not be calculated. These exclusions and the functional unit combined result in the system boundaries. Then, a decision is made on which impact categories are included. An impact category is focused on a specific environmental effect and presents part of the total outcome. Examples of such categories are:

- Global Warming Potential (GWP), the impact caused by greenhouse gases
- Human Toxicity. This is an impact category focusing on toxic substances to the human body. These are divided in cancer and non-cancer related substances;
- Acidification. Of water or soil, caused by the release of certain gases;
- Eutrophication. A process where the aquatic environment is enriched with nutrients. This results in excessive growth of certain plants and lowers oxygen-availability for other species; and
- Ozone depletion. This indicates how much the ozone layer is affected.

Many more categories besides the above are possible. For each category the values from the inventory are expressed in emissions suitable to this effect. For example, ozone depletion is expressed in kg Chlorofluorocarbon and GWP in kg carbon dioxide (CO_2). However, within one impact category, more substances can be associated. For example,

methane fits in the GWP category as well, due of its' similar environmental effect. Therefore the impact of such other emissions are calculated according to their equivalent CO_2 value (CO_2e). In the case of methane, 1kg equals 25kg of CO_2. The result of one impact category is thus the summarized consequence of multiple substances that have an effect on the same outcome.

3.2.2 Inventory

This is the most time-consuming phase as it comprises the data collection. The life cycle inventory essentially is a list of all types and quantities of resources used. This data can be obtained via invoices, observation, or measurements.

3.2.3 Impact assessment

After all resources are mapped out and the inventory is complete, impact can be quantified. This means actual values can be linked to the amount of resource usage. Depending on how the energy is obtained and generated, the use of 1 kWh electricity could be translated to 0.6kg CO_2, for example.

3.2.4 Interpretation

Assessing outcomes can be done during the analysis, but most conclusions can only be drawn at the end. The following questions are frequently considered:

- How high are the emissions?
- How does this relate to other products/services in this sector/company?
- What are 'hotspots', i.e. biggest contributors to the overall impact?

4 Methods

4.1 Research goal and analysis approach

The goal of this research is to find all costs and health burden associated with the GWP of the TDM-pathway for kidney transplant patients and to compare these values for DBS and WB sampling. Included are the usage and end of life phase. System boundaries are presented in figure 5. Upstream activities (production, procurement and transport of goods) are excluded in this research because of; 1) confidentiality, 2) time constraints and 3) the fact that quick(er) wins are possible in the included parts. A consequential approach will be used, meaning the marginal impact of one additional functional unit is calculated. In this research, the functional unit is the care pathway for one AUC. This is a convenient unity as professionals encounter it on a daily basis and it is a typical measure for the type of patients in this research. Moreover, some resources are only applicable for a total AUC and no less. That makes a total AUC more feasible than for example 2 tubes or spots of blood. The base case is a one-year analysis for thousand patients for whom an AUC is needed. To investigate sensitivity of certain parameters, various one-way sensitivity and scenario analyses are conducted. After that, a Probabilistic Sensitivity Analysis (PSA) with a time horizon of fifteen years is executed. The PSA is done to calculate decision uncertainty. The time horizon of 15 years is used because this corresponds to the available data on kidney transplant survival [51]. This data is used to determine the amounts of years each patients' graft functions.

As mentioned before, DBS sampling is a validated analytical method and considered

equally suitable in assessing medication concentrations as WB sampling [31] [32] [33]. Evaluating the direct effectiveness or reliability of the method is thus not necessary. A cost-minimisation might therefore be suitable. However, other effects like the environmental impact is not taken into account in the previous mentioned studies. This impact can be presented in human health outcomes. Being a healthcare-related study, using health outcomes is preferable to other outcomes. The relation between GWP and health outcomes is a conversion factor provided by Tang et al. [52]. This conversion factor represents the Disability Adjusted Life Years (DALYs) associated with the emission of one kg CO_2e . DALYs represent the number of life years lost due to illness and early death [21].

$$DALY = YLL + YLD$$

YLL represents the years lost to premature death. This is the difference between the age of death and expected life expectancy. Life years lived with the disease or condition are of less quality than life in full health. These years are assigned to a factor between 0 and 1. Multiplying this factor with the affected years lived gives *YLD*. Calculating DALYs makes it possible to compare health outcomes for WB and DBS. For interpretation purposes, DALYs are monetised in the final results based on valuation factors from Committed to the Environment (CE) Delft [53]. Therefore, this study is a CBA. Based on CE Delft, each DALY can be assigned a monetary value. A lower and upper limit of €50,000 and €100,000 respectively is advised. They also propose a central limit of €70,000, which will be used in this study. Final results are calculated using the net monetary benefit (NMB) approach of a CBA. The NMB is the absolute difference in costs and benefits between two alternatives. The formula is:

$$(C_{DBS} - C_{WB}) - (B_{DBS} - B_{WB})$$

Where C are costs and B are benefits. Classical CBAs typically use outcomes that are 'positive'. This means, a higher value is beneficial, such as revenues or QALYs gained. However, in this study DALYs are used, which are 'negative'. Therefore, the used formula in this study is:

$$(C_{DBS} - C_{WB}) + (B_{DBS} - B_{WB})$$

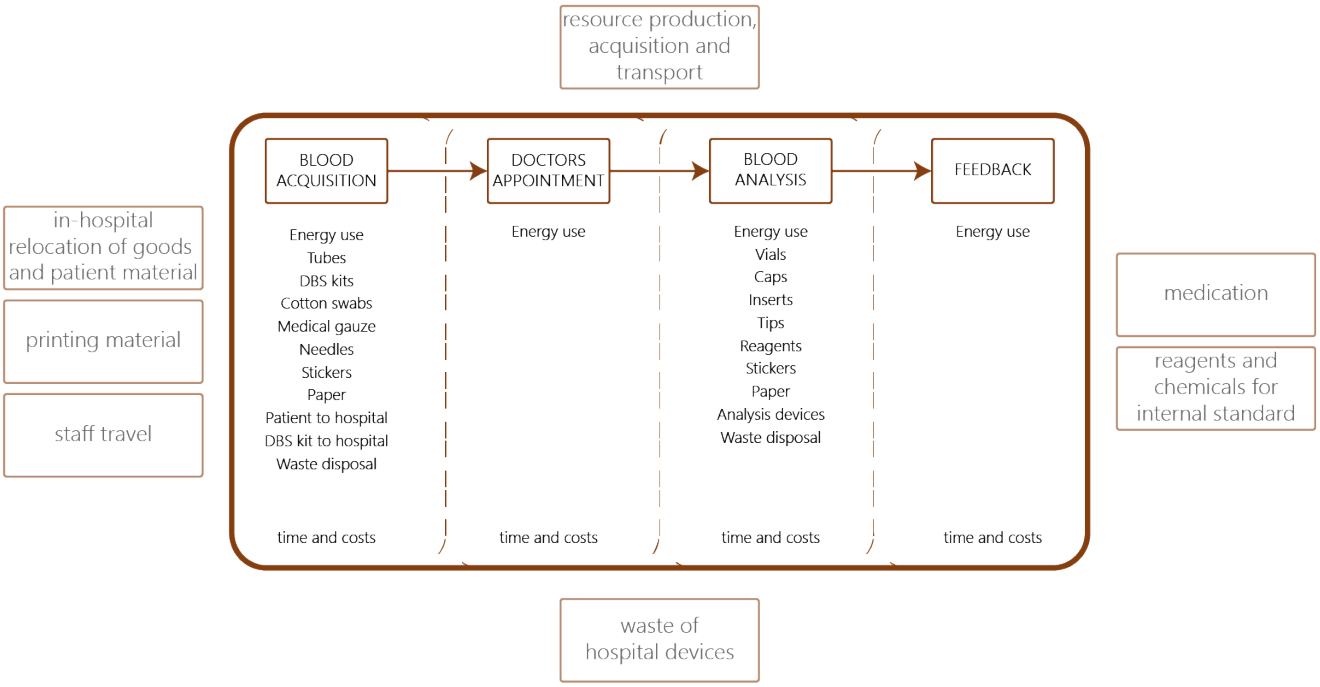
First, pathways for both methods (WB and DBS sampling) are explored and investigated through shadowing of involved professionals. During the shadowing process, all steps of TDM and used resources are observed and listed. Where possible, the needed time for steps in each stage is determined as well.

As the number of samples differs for each AUC, calculating resource use per AUC directly is not possible. Resource use is therefore calculated per sample. Although the number of blood samples are indicated in table2, these values do not correspond with actual numbers. This can have multiple reasons, as sometimes;

- An AUC is needed over a longer time period, which requires more samples;
- A sample is analysed twice as a verification;
- Samples are not taken on all indicated times;
- A delivered sample is not analysable.

Actual numbers on samples per AUC are calculated by exporting and combining annual data for TAC, EVER, CIC and MPA from GLIMS. For each patient, the number of results on one day is used to make an estimate on the number of samples for an AUC per medication type.

Figure 5: System Boundaries



All lighter grey items above, below and besides the brown square are excluded in this study

4.2 Costs

In this study, costs are based on a societal perspective and thus include costs for the hospital, patient and society. A combination of bottom-up and top-down microcosting is used, meaning resource use is derived for each stage on a detailed level (microcosting) and costs per unit either by hospitals-specific or national tariffs (bottom-up and top-down respectively) [54]. Resource use and unit costs are based on data from 2021. Total costs are calculated by multiplying resource use with unit costs. In the PSA, costs are discounted at a rate of 4%, based on recommendations from the cost manual [22].

Resource use per AUC is based on observation, consultation of professionals and data from 2021 obtained from GLIMS and HiX. Usage of consumables, such as needles or pipettes, is observed in 2022. Although this is not in the same year as the provided data, there are no issues concerned as the same materials were used in 2021. Time spend by hospital staff in all steps are obtained by using reports, observation using a stopwatch or consulting an expert. The time patients spend in the hospital for WB sampling is based on the number of samples taken for one AUC. The time patients spend on executing the DBS sampling is estimated based on own experience. The time needed to send the kit to the hospital is neglected as it is assumed the patient combines this task with other activities. The time patients travel to and from the hospital is based on distances calculated with postal codes of transplant patients, obtained via HiX. Although the driving speed depends a lot on the distance to be travelled, an average velocity of 60 km/h is assumed.

Prices per kg waste are provided by the Waste Manual for Dangerous waste from the LUMC [55]. Unit prices for consumables are partly provided by the hospital and otherwise searched for on the internet on websites of common suppliers. The recommended order quantity is used to find reasonable purchasing costs per unit. Shipping costs per

unit are neglected as different goods from one supplier are usually purchased within one order, meaning the marginal costs per sample are only very small.

Costs for yearly maintenance on devices are derived from the hospital's management software Ultimo. Dividing these totals by annual usage gives the cost per sample.

Hourly tariffs for hospital staff are obtained from the financial department of the LUMC. Productivity losses are calculated using the Human Capital Approach (HCA), which means associated costs are derived from hourly labour costs multiplied with the hours an individual is absent [56]. Hourly costs are based on the Dutch manual for cost analyses [22]. Another method to calculate productivity losses is the Friction Method, which uses the time needed to replace an individual as a measure of lost productivity. This can be more suitable in some cases, as the missed working hours don't necessarily represent the missed work when this can be cancelled or a colleague is able to take over the tasks. However, as the productivity losses in this case don't concern long-term absenteeism, HCA suffices.

Patient costs for travelling were calculated using the calculated distances to the hospital, multiplied with costs per km. These costs were calculated using data from the General Dutch Cyclists Union (ANWB) [57] on general car costs per km and Statistics Netherlands (CBS) [58] for average fuel costs per liter. Travel is also considered as productivity loss, using the same distance calculations.

Costs associated with sending the kit to the hospital are considered as societal costs and are derived from website of the national postal service (PostNL) [59].

4.3 Environmental impact and health outcomes

To obtain DALYs for both methods, first a carbon footprint is calculated. Global warming is a tangible and topical subject worldwide, so the carbon footprint or GWP lends itself as a suitable instrument to communicate environmental impact. Besides that, a carbon footprint is easily compared to available data such as the total carbon footprint of the LUMC [60] or carbon emissions from other literature that refers to GWP in a health-related context [24] [26] [46] [61]. The footprint is calculated based on resource use and emission factors. In the PSA, effects are not discounted, as the used value is already based on a calculation for a time horizon of 100 years [52].

Energy and water consumption per sample is calculated as follows. Annual energy and water consumption of the relevant building of the LUMC is divided by its' surface area to obtain the energy use per square meter per year. The surface area of the lab is estimated using a tape measure. As one part of the lab consists of working space with flexible workstations for multiple people, the surface area is assumed to be representative for the blood acquisition department and the doctor's office as well. GLIMS figures on total annual laboratory results for all examination types are used to calculate the percentage lab usage by TDM examinations. Energy consumption per sample is then calculated by dividing the total annual energy use of TDM by the total number of kidney transplant TDM samples examined 2021.

Waste generation per sample is calculated by weighing all resources on a scale. Although many resources are very lightweight, the values are assumed to be accurate as a milligram scale from the lab is used for measuring.

Reagents consumption per sample is derived from the analysis protocols used in the lab [62] [63] [64] [65] [66] [67]. Travel distance for patients is calculated using postal codes obtained from HiX, as previously described.

CO_2-emission values per unit measure for electricity and (waste) water are derived from the yearly energyreport of the LUMC [68] and CO_2 emission factors [69]. Emission values for natural gas, diesel oil and waste are derived from the civil service for Dutch entrepreneurs (Rijksdienst voor Ondernemend Nederland, RVO) [70]. These values are not provided in CO_2-equivalents, but for CO_2 itself only. After consulting a professional from RVO, the contribution of other GHG's was stated to be negligible. Carbon emissions from district heating are neglected as this is residual heat and already accounted for in other sectors [71].

Due to commercial confidentiality, especially (impact) data for reagents and pharmaceuticals is hard to obtain. This is a problem more often encountered in this subject area [26] [72]. Moreover, the differences within types of reagents can be huge, as the (complexity of) synthesis steps varies substantially [73]. Estimations on emission factors for pharmaceuticals were made by McAlister et al. [26], but these values are focused on the production phase only, which is beyond the scope of this research. Besides this, all resource types are made of different material and thus have different carbon emissions. Therefore average emission factors for waste incineration from RVO are used [70]. Emission factors of waste transport are estimated based on emission figures provided by Committed to the Environment (CE) Delft [74], taking values for medium-heavy transport in vehicles without a trailer and a gross vehicle weight of >20 ton [75]. Transport distance is calculated based on expert knowledge of transhipment and processing locations. Reports from the LUMC suggest 30% of all waste is recycled. However, for special hospital waste (SZA), this is not the case, as this is always incinerated. Since not all waste is collected at the same place, it is hard to know for sure whether the waste is correctly separated. All waste was therefore assumed to be incinerated in the base case.

Emission factors for patients' travels to the hospital are based on average emission figures per kilometer, derived from the Dutch association for sustainable entrepreneurship [76], multiplied with the calculated distance based on postal codes.

Emission factors for transport, to calculate the emission associated with sending the DBS kit to the hospital, are derived from previous literature [77]. As the given value encompasses emissions from a local depot to the home delivery, each AUC is assumed to emit four times this value (two times for local depot $\leftrightarrow$ patient and two times for local depot $\leftrightarrow$ hospital, as the kit needs to be sent from the hospital to the patient and back).

5 Results

5.1 Care pathway and resource use

During the shadowing process, each phase of TDM-pathway is investigated to collect necessary info on consumable use. Phases are previously discussed and presented in section 2 and figure 2 respectively. Used resources per medication type for WB and DBS are presented in table 3.

Table 3: Resources and their amounts used per sample (or mentioned otherwise) for TEC (TAC, EVER, CIC) and MPA for WB and DBS

	WB		DBS	
Consumable	TEC	MPA	TEC	MPA
EDTA Tube	1	1	-	-
Serum tube	-	1	-	-
Phlebotomy needle	1	1	-	-
First AUC needle	1 per AUC	1 per AUC	-	-
First AUC needle plastic wrap	1 per AUC	1 per AUC	-	-
Medical gauze	1	1	-	-
Cotton pad	1	1	-	-
Plastic seal kit	-	-	1 per AUC	2 per AUC
Plastic return bag DBS	-	-	1 per AUC	1 per AUC
Return envelope	-	-	1 per AUC	1 per AUC
DBS cards	-	-	1	2 per AUC
DBS HemaXis kits	-	-	1	2 per AUC
Safety lancet	-	-	1	1
Vial insert	-	-	1	1
D200 tip	1	2	1	1
Ep-tubes	1	1	1	1
Vials	1	1	1	1
Caps	1	1	1	1
Paper sheet	1 per AUC	1 per AUC	±4 per AUC	±4 per AUC
Big sticker	1	1	1 per AUC	1 per AUC
Small sticker	-	-	1	1

TAC: Tacrolimus, EVER: Everolimus, CIC: Ciclosporin, MPA: Mycophenolic Acid, WB: Whole Blood sampling, DBS: Dried Blood Spot sampling. *As the AUC is combined with acquisition for other tests as well, wich requires more tubes to be drawn, a more comfortable needle is used for the first timeslot.

5.2 Base Case

Costs, GWP and DALYs are calculated in the base case for thousand patients. All patients go through the care-pathway for one AUC.

The main factor influencing overall outcomes is the number of samples per AUC. As the most common number of examined samples is four, this value is used in the base case. As mentioned before, a medication schedule including MPA implies more resources to be used and analyses to be done. This makes it an important factor to take into account in the base case. Based on obtained data, 60% of the patients have a medication combination with MPA, which is therefore used in the base case as well. All base case variables and values are presented in table 4. For the sake of clarity, consumable prices are combined to obtain a price per sample for each medication type. This also applies to emissions. An overview of all individual costs and used emission factors can be found in appendix A.

Table 4: Resource use, costs and emissions used in the Base Case

Resource use per AUC	Use	Unit	Source
Regular samples	4	tubes/spots	GLIMS
MPA samples	4	tubes/spots	GLIMS
Distance to hospital	35	kilometer	HiX
Time per kilometer	0.01	hour	assumption
Consult time	0.5	hour	expert opinion
WB time analyst	0.1	hour	reports
WB time blood 1 sample	0.08	hour	observation
WB extra time physician assistant	0.25	hour	expert opinion
WB time pharmacist	0.08	hour	expert opinion
DBS time analyst	0.11	hour	reports
DBS time blood 1 sample	0.17	hour	observation
DBS extra time physician assistant	0.08	hour	expert opinion
DBS time pharmacist	0.12	hour	expert opinion

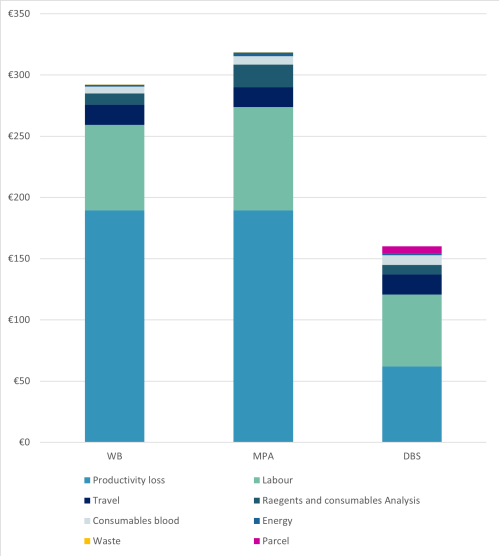
Resource	Costs	Per	Source	kg CO_2
Analyst	€38	hour	LUMC	
Phlebotomy technician	€39	hour	LUMC	
Physician assistant	€39	hour	LUMC	
Pharmacist	€81	hour	LUMC	
Productivity losses	€34.75	hour	cost analysis manual	
Only analysis	€2.33	sample	various	1.22
WB consumables	€3.72	sample	various	1.38
MPA consumables	€4.05	sample	various	1.41
DBS consumables	€2.53	sample	various	1.24
AUC WB consumables	€1.43	curve	various	0.25
AUC MPA consumables	€1.43	curve	various	0.25
DBS kit	€5.01	curve	various	0.53
DBS variable consumables	€0.18	1 sample	various	0.03
Hospital kit delivery	€3.84	parcel	postnl	0.36
Patient 1kit delivery	€1.92	parcel	postnl	0.36
Patient 2kit delivery	€2.88	parcel	postnl	0.36
Travel	€0.31	patient kilomter	ANWB, CBS	0.20
Parking ticket	€5.5	sample	LUMC	

Hospital kit delivery: costs associated with sending the kit to the patient. This is always done per two kits and therefore only one amount applies. Patient 1kit delivery: costs associated with sending 1 kit to the hospital. Patient 2kit delivery: costs associated with sending 2 kits to the hospital. The amount of kits sent to the hospital depends on the amount of samples needed. Costs differ due to different parcel weights. Detailed overview of all individual costs can be found in appendix A

Costs and emissions per AUC as used in the base case are shown in figures 6 and 7 for WB, MPA and DBS. MPA values represent an AUC for which MPA is combined with another medication type, like TAC, EVER or CIC. As mentioned before, this requires extra consumables and analyses. Total costs are €292, €318 and €160 for WB, MPA and DBS respectively. Most costs are related to productivity losses and labour costs in all cases. However, productivity losses are nearly three times as high for WB and MPA than for DBS. No parcel costs are associated with WB and MPA, as nothing has to be sent to an from the hospital. It is noteworthy that waste production hardly contributes to overall costs for all three options. Although to a lesser extent, this applies to the emissions as well. For WB, MPA and DBS, total emissions are 11.6, 16.3 and 12.3 kg CO_2e respectively. Patient travel and energy consumption accounts for most emissions. These values are comparable for WB and DBS, although energy consumption for MPA is notably higher.

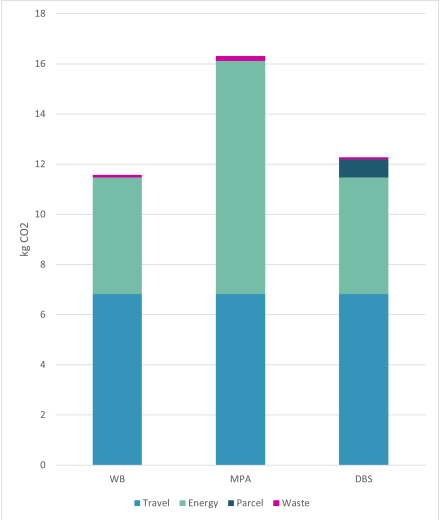
Results of the base case are presented in figures 8, 9 and 10. Base case results suggest total costs, emissions and DALYs are all higher for WB than for DBS. Only society emissions and DALYs are higher for DBS, due to the delivery of the DBS kit from and to the hospital. Total costs for WB are nearly twice as high as DBS, mainly due to higher society costs. Total emissions and DALYs are almost 20% higher for WB than DBS, due to higher hospital emissions. As these values are in favour of DBS, the NMB result is negative. For interpretation purposes, results will be presented positive when in favour of DBS and negative when in favour of WB. Saved costs and averted DALYs are presented in table 5. Based on the base case, total cost savings after one year for thousand patients are €155,641. During this period, 0.003171 DALYs are averted which corresponds to savings of €222. This results in a NMB of €155,862.

Figure 6: Costs per AUC



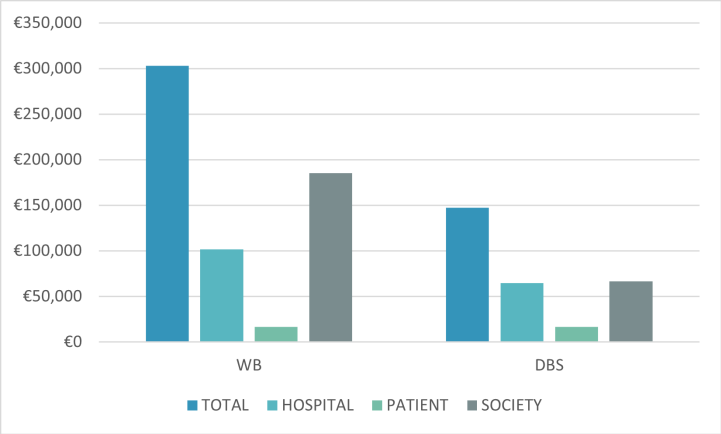
Costs in € per AUC. Productivity losses and labour costs have the greatest share.

Figure 7: Emissions per AUC



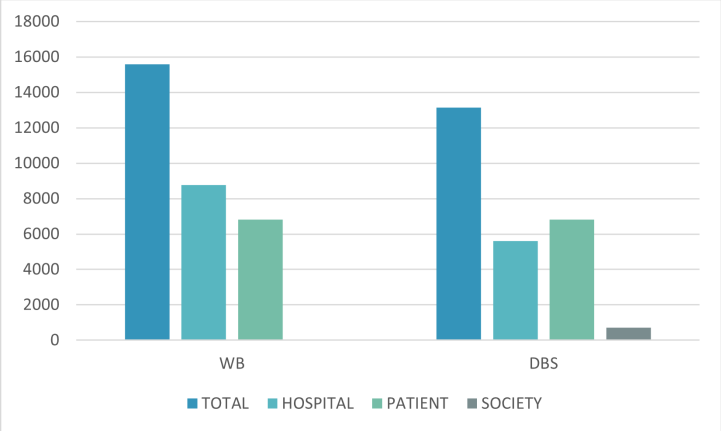
Emissions in kg CO_2e per AUC. Patient travel and energy use accounts for the most emissions.

Figure 8: Base Case - Costs



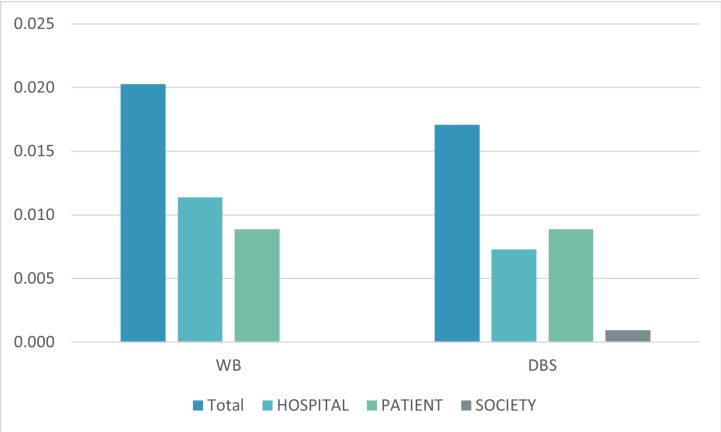
Costs for one-year. Analysis for thousand patients of the care pathway for an AUC.

Figure 9: Base Case - Emissions



One-year results for thousand patients of the care pathway for an AUC. Emissions are shown in kg CO_2.

Figure 10: Base Case - DALYs



One-year results for thousand patients of the care pathway for an AUC. DALYs are calculated from emissions using the conversion factor from Tang et al.

Table 5: Saved costs and averted DALYs in the base case

	Costs saved	Saved emissions (kg CO_2e)	Averted DALYs
Total	€155,641	2440	0.003171
Hospital	€36,880	3164	0.00411
Patient	0	0	0
Society	€118,761	-724	-0.000941

A negative sign means costs and/or emissions are higher for DBS. Total saved emissions and averted DALYs are lower than hospital savings, due to higher emissions and less DALYs averted in the society part.

5.3 Sensitivity analyses

Sensitivity analyses are executed to find out main drivers of the NMB. Seven variables are considered for a one-way analysis and two scenario cases are presented to investigate the impact of changing multiple variables at once. The following analysis are performed:

1. Waste emissions.
   As mentioned previously, LUMC reports suggest 30% of all waste is recycled. Therefore we examine the impact of a 30% reduction in carbon emissions of 1 kg of waste. To investigate the impact of higher emissions as well, emissions are increased by 30% as well.
2. Energy consumption.
   The LUMC has ambitions to use green energy for 80% of their electricity consumption, which would reduce carbon emissions due to energy use. This is mimicked by multiplying electricity emissions to 20%. On the other hand, emissions due to energy consumption may rise. This may happen because of the war currently going on in Ukraine. Coal is used to compensate the gas shortage caused by the war, which causes double emissions for the same amount of electricity generation [78]. The Netherlands are said to be dependent on Russian gas for 15-20% [79] [80]. Thus, the emissions due to energy consumption are increased by 20% as well.
3. Driving emissions.
   As the world becomes more and more aware of global warming and the environment, sustainability measures like electrification are more and more common, especially for cars. Literature suggests this can lower emissions with 50% or even more [81] [82]. However, depending on the electricity grid, carbon emissions per kilometer may also be higher, according to Neugebauer et al. [83]. They calculated emission ratios for five scenarios with different electricity grids. Their findings are used to evaluate the difference in emissions for electric and combustion travel. Emissions for patient travel and parcel delivery are first multiplied with the lowest and afterwards with the highest emission ratio. The lowest ratio is in favour of electric cars and the highest of combustion cars. The ratio will not be applied to waste transport, as trucks are less likely to become fully electric in the near future.
4. MPA analysis.
   As mentioned before, the use of MPA in combination with other medication types has implications for amount of consumables used and requires additional analyses to be done. To assess the impact of MPA on costs and emissions, all extra MPA use was set to zero. Although currently not possible, this mimics the hypothetical situation where MPA doesn't need extra consumables or analyses.
5. Patient travel.
   As shown in the base case, DBS sampling is already time saving for the patient. However, he or she still must go to the hospital for the consultation only. If this

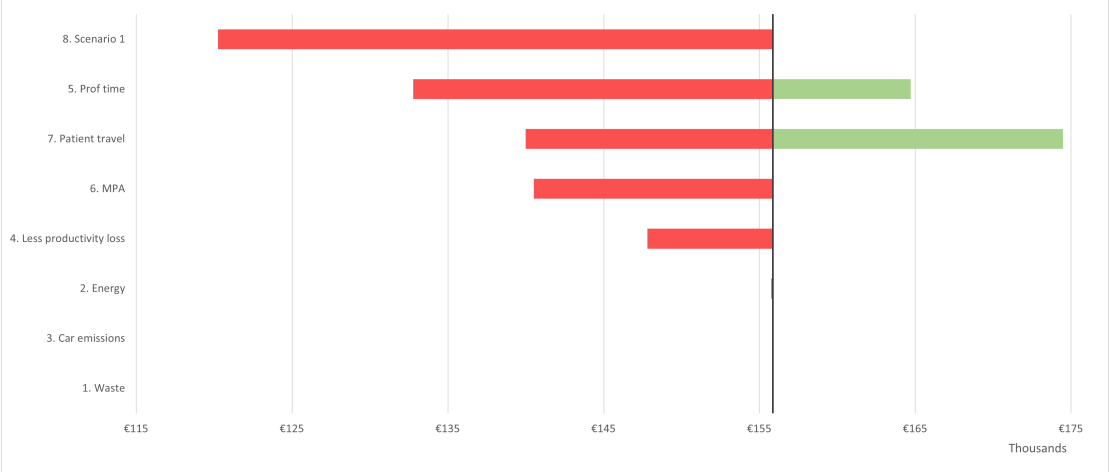
could be a video-consultation, even more time, costs and emissions will be saved. Some patients will still have to go to the hospital for other types of appointments. Therefore, the impact of 50% of the patients staying home for an online consult is calculated. On the other hand, a longer driving time is considered as well. Driving to and from the hospital on top of waiting several hours during blood sampling is more exhausting for patients living further away. Patients living further away might therefore be more eager to use DBS or more likely to be asked by the doctor. Therefore, the distance to the hospital is multiplied with a factor 1.5 for DBS.

6. Productivity loss.
   All patients' time is calculated as productivity losses. However, some patients might not be working anymore, which means productivity losses are not applicable. According to literature, between 5 and 7% of kidney transplant patients is above 65 years of age [84] [85]. Although the retirement age in The Netherlands is currently 67, we assume 7% this is a realistic value to account for the people not working (anymore). Therefore, only 93% of all patients is assumed to be working for this analysis.
7. Professional time.
   Some patients get confused when sampling their blood with DBS or are scared to make mistakes. The physician assistant then needs to clarify the instructions, resulting in extra labour costs and productivity losses. Besides that, a confused patient may assign doubtful time stamps to the spots or provide contradicting information about the medication schedule. This makes calculating the AUC complex, which means the pharmacist needs more time as well. As it was hard to obtain a clear time frame on how much time the physician and the pharmacist then spend, extra physician time was tripled and the pharmacist time was doubled to investigate the cost consequences of such a scenario.
8. Scenario 1: Extra time and resources.
   The analysis outlined above describes how more time is sometimes spend by the physician assistant and/or pharmacist. Besides that, the patient may need extra kits to obtain the right number of spots. Therefore, a scenario of more time for the professionals and more resource use is investigated.
9. Scenario 2: War.
   Considering the current war in Ukraine, a rapid increase in prices can be observed. Besides that, the war results in a shortage on gas, which results in The Netherlands allowing more coal to be used for generating electricity. Coals emit roughly twice as much carbon [78] as gas for the same amount of energy. Given these circumstances, for this scenario fuel prices are doubled compared to the 2021 average and gas emissions are increased by 20%.

A tornado plot of all sensitivity analyses is shown in figure 11. Main driver of the NMB is the extra time spend by professionals, represented by analysis five and eight. Other factors with main impact are patient travel and the need of extra resources and analysis for MPA. More costs could be saved when patients don't need to travel and when professionals need less time. The energy composition, car emissions and amount of waste have only very little impact on the NMB. Saved costs and averted DALYs for all analyses compared to the base case are shown in table 6. As can be seen, costs are saved in all sensitivity analyses, meaning DBS is cheaper than WB. However, the use of DBS does not always mean DALYs are averted. This is the case when no extra consumables and analyses are needed for MPA and when patients need to travel further for DBS. Despite the fact that less DALYs are averted in these cases, the NMBs remain positive. Nevertheless, NMBs for the sensitivity analyses can be more than 35 thousand euros

lower, which is the case for scenario one. Lower NMBs are denoted with a negative value in the rightmost column.

Figure 11: NMBs for sensitivity analyses



Tornado plot with NMBs for all sensitivity analyses. Main drivers are productivity loss, patient travel and the extra resources and labour needed for MPA. The type of sensitivity analysis is denoted with the corresponding number.

Table 6: Saved costs and averted DALYs for all sensitivity analyses

Analysis	Costs saved	Averted DALYs	NMB	NMB - BC
Base Case	€155,641	0.00317	€155,863	
(1) Waste x0.7	€155641	0.00316	€155,862	- €0.98
(1) Waste x1.3	€155641	0.00319	€155,864	€0.98
(2) Electricity 80% green	€155,641	0.00148	€155,744	-€118.61
(2) Coal instead of gas	€155,641	0.00338	€155,877	€14.63
(3) Low car emissions	€155,641	0.00371	€155,900	€37.55
(3) High car emissions	€155,641	0.00302	€155,852	-€10.54
(4) No extra consumables and analyses for MPA	€140,569	-0.00073	€140,518	-€15,344.85
(5) No travel DBS	€173,945	0.00761	€174,478	€18,615.12
(5) Further travel DBS	€140,086	-0.00126	€139,998	-€15,865.12
(6) No extra physician assistant and pharmacist time	€147,796	0.00317	€148,018	-€7,844.81
(6) Longer extra physician and pharmacist time	€164,487	0.00317	€164,709	€8,845.83
(7) Less productivity loss	€132,549	0.00317	€132,771	-€23,091.67
(8) Scenario 1	€120,144	0.00149	€120,249	-€35,614.19
(9) Scenario 2	€155,641	0.00338	€155,877	€14.63

Saved costs, averted DALYs and NMB compared to the base case. The corresponding number of the sensitivity analysis is denoted by (x). Abbreviations: NMB: net monetary benefit; BC: base case.

5.4 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis is executed to calculate decision uncertainty. As mentioned previously, a time horizon of 15 years is used, corresponding to available data on graft survival. Table 7 shows the uncertainty concerning variables and their distributions used in the PSA.

Table 7: Variables and their used values in the Probabilistic Sensitivity Analysis

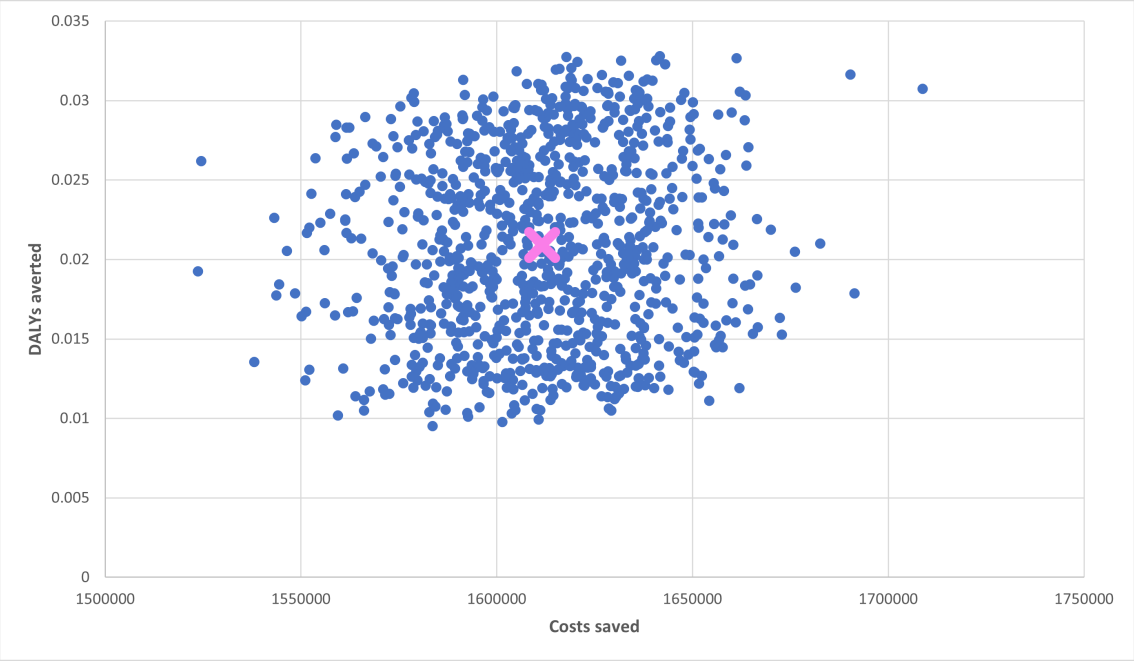
Variable	Base case value	Par 1	Par 2	Distribution	Source
Number of samples*	4	-	-	empirical	GLIMS
Distance to hospital	35	1.05	32.92	gamma	HiX
WB time analyst (h)ˆ	0.1	0.45	0.4	gamma	documentation
WB time blood 1 sample (s)	288	600	100	normal	observation
WB extra time physician assistant (s)	900	600	100	normal	expert opinion
WB time pharmacist (s)	288	330	50	normal	expert opinion
DBS time analyst (s)	396	405	157	normal	documentation
DBS time blood 1 sample (s)	612	600	100	normal	experience
DBS extra time physician assistant (s)	288	1050	250	normal	expert opinion
DBS time pharmacist (s)	7.2	600	100	normal	expert opinion
Emission patient travel	0.2	0.08	0.23	uniform	[70] [83]
Emission parcel delivery	0.72	0.31	0.84	uniform	[83][82][81]
Emission energy	1.16	0.62	1.23	uniform	[68][80][78]

*Details of how the number of samples is distributed can be found in the supplemental materials. ˆ Only distribution parameters for the analyst time for WB is in hours, as enough data was available to give a reliable distribution. Other durations were assumed to have a normal distribution. The use of seconds instead of hours prevents negative estimation values being drawn from these distributions. Abbreviations: (h) = values presented in hours; (s) = values presented in seconds; Par = parameter

Figure 12 shows the results of the PSA, with a mean NMB of €1,611,567.88. From the PSA results, also a minimum NMB of €1,525,042.07 and a maximum NMB of €1,710,874.59 can be found. In order to compare these values with the base case, the base case result is extrapolated to 15 years, using the same discounting rate of 4%. This results in an NMB of €1,732,934.10, meaning results of the PSA are 0.99 to 0.88 times lower. This difference has several reasons. Firstly, uncertainty regarding some variables causes changes, as can be seen in section 5.3. Moreover, survival curves of kidney transplants are incorporated in the PSA, meaning each year more and more patients are not part of the simulation anymore. And finally, the number of samples is set to four in the base case, while an empirical distribution is used in the PSA. This will account for changes as well. Nevertheless, the results show that some uncertainty remains.

Mean costs saved, mean CO_2 emissions and DALYs are presented in table 8. Total cost savings are more than 1.5 million euros. This corresponds to 3% of the targeted savings [34]. This may seem like a low value. However, considering the wide range of different activities, procedures and timeframe the savings are to be realised, it is a significant contribution to the total value. Emitted cabon savings are slightly more than 16,000 kg CO_2e. This relates to roughly 2% of total carbon emissions of the LUMC, extraopolated to 15 years [60]. These savings are equivalent to producing over 38 thousand avocados or flying from New York to Amsterdam 9.75 times [86].

Figure 12: Plot of the PSA



Graphic presentation of PSA results. Each dot represents one of thousand runs of the PSA. Each run consists of a cohort of thousand patients, run for 15 years.

Table 8: Mean costs, emissions and averted DALYs in the PSA

	WB	DBS	Saved
Costs	€3,329,276	€1,717,708	€1,611,568
Emissions	165,859	149,769	16,090
DALYs	0.2156	0.1947	0.0209

6 Discussion

6.1 Results

In this study, the financial and environmental impact of TDM using WB and DBS sampling is determined for the first time. Main outcomes are that total costs, emissions and DALYs are higher for WB than for DBS. This results in a net benefit in favour of DBS. Main cause for the cost difference are higher productivity losses, due to multiple hours of waiting in the hospital for patients using WB sampling. Another reason for higher hospital costs are medication combinations with MPA, due to extra consumables and analyses associated with these medication plans. Emissions and DALYs are also higher for WB due to MPA. The extra needed consumables and analyses for a combination with MPA cause higher emissions due to more energy consumption and waste production.

As the time spend by professionals is a main driver of the NMB, optimising the workflow to make sure professionals can be as productive as possible would be beneficial. One way to tackle this is by improving DBS instructions and self-reliance of patient. As can be read in section 5.3, a lack of understanding or independence of a DBS patient may result in more work for the professionals. Patient travel also has a significant impact. Allowing DBS patients to have an online consult will have a major impact on the NMB

as well. Online consultations will also directly have reduce productivity losses, as the travel time is no longer an issue.

Results of this study correspond to other literature with respect to the lower costs for DBS [42] [43]. However, compared to this literature costs per AUC seem to be slightly underestimated. Mainly laboratory costs are much lower in this study. The reason for this is probably the fact that other articles took the maximum national tariff as costs for the analysis, while analysis costs in this study are calculated based on consumables only.

Also, energy use per sample is quite different compared to other literature [46] [26]. This has implications for the CO_2-emission per sample. The reason for this difference is not clear, since not all characteristics of the labs in the mentioned articles are described. One of such characteristics is the variety and number of devices used in the lab. This may account for a big difference, as some laboratory devices like a microscope hardly use any energy, while others (like the LC-MS/MS device in the LUMC) consume a lot. Besides this, detailed department-specific information is desired to make a fair comparison between energy consumption of this and other studies. Such details are currently not available but could for example be obtained with a power meter. Especially since energy consumption accounts for a large if not the biggest amount of emissions [50].

6.2 Relevance and limitations

Results are mainly of value for hospitals not using DBS (yet). The study shows DBS is cheaper and associated with less DALYs than WB, which means these hospitals can benefit in terms of costs and environmental impact as well. Hospitals currently using DBS could use the results as a benchmark and evaluate whether adaptations are in place to improve their processes. Results might also be of value for the implementation of DBS for other purposes than TDM. Blood analyses are required for many more diagnostic and therapeutic activities, which means DBS could potentially save money and avert DALYs in these areas as well.

However, results must be adopted cautiously, as some limitations arise because not all aspects of the care-pathway are included in this study.

Firstly, only the marginal impact of an additional AUC is calculated. This means that 'basic' devices and supplies are assumed to be already present and therefore not considered in the analysis. This applies for example to the procurement of computers and analysis devices, but also extra analyses done for internal quality control or 'proficiency testing' are left out. All these things are associated with additional resource use, energy consumption and/or labour. Thus, if one wishes to determine the total financial and environmental impact of the process as a whole, the above mentioned factors should therefore be considered as well.

Total carbon emissions are converted to DALYs to estimate impact on human health. Although based on carefully calculated conversion factors by Tang et al. [52], the actual value of DALYs may differ due to multiple reasons. Firstly, the conversion factor is calculated for three different scenarios. In each scenario other assumptions regarding economic growth are made. Tang et al. assume less DALYs with greater economic growth, as future innovations might be able to prevent environmental change or lower its' impact on human health. Given the high inflation rate at the moment, the factor with the lowest economic growth is used. However, as the other scenarios assume less

DALYs per kg, the amount of DALYs might be overestimated in this study. On the other hand, only DALYs associated with carbon emissions are considered. If other impact categories besides GWP would be considered as well, DALYs would be higher. For example, various chemicals are used for the WB and DBS analysis. If such chemicals leak into the freshwater system, human health will be affected which will result in more DALYs. Future studies could therefore calculate the DALYs for multiple scenarios and/or include multiple impact categories to obtain a more accurate value.

The PSA is calculated for 15 years because this is the usual timeframe to present survival curves for kidney transplants. However, even though survival rates were incorporated, grafts may last longer than 15 years. Also some probability distributions used in the PSA might not represent completely reliable values. As these are currently based on small data sets, expert opinions or estimations, obtaining more data for higher accuracy is recommended. This applies in particular to the time spend by professionals.

6.3 Challenges

Although environmental impact is incorporated as health outcomes in the current study by converting CO_2e to DALYs, actual environmental impact is easily overlooked. As the value of averted DALYs is not even near 1% of the saved costs, saved carbon emissions (from which the DALYs are obtained) hardly impact the NMB, while the actual amount saved is noteworthy. Thus, despite we are aiming to address environmental impact in this study, the way the results are calculated determine how seriously it will be taken. The difference in saved carbon emissions is presented in appendix B. As can be seen, the whole order of main drivers is changed compared to figure 11. Now professional time or productivity losses are not the main drivers of the outcome anymore. Instead, patient travel, MPA and the energy composition have the most influence. This means the focus to minimise impact would be on completely different parameters. This difference shows exactly the problem that must be addressed. It shows that the focus we have on certain outcomes allows other negative effects to happen we might be unaware of on forehand. This is the dilemma we are currently facing regarding environmental impact versus our goals as a society. It is no question anymore that we must act to limit climate change and prevent more environmental harm. The question is whether we allow ourselves to criticise and change the way we assess and judge our activities. If we are able to change the way in which we value our environment and the closely related health, we might be able to keep providing health in the long run as well.

6.4 Conclusion

To summarise, this study shows DBS sampling saves cost and reduces environmental impact compared to WB sampling. Future research should focus on obtaining data with higher accuracy, although investigating whether DBS could be beneficial for purposes other than TDM will be of value too. Besides that, this study shows we must think twice about how we value our environmental, as looking at costs and health outcomes only drastically underestimates the potential impact. Considering the limited research available into the environmental impact of healthcare-related activities, this study adds to the much needed data and literature on the subject.

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A Appendix - Detailed overview of all used costs and emission factors

Product	Price	Source	CO2	Source
Consumables				
EDTA Tube	€0.317	merkala	*	*
Serum tube	€0.380	merkala	*	*
Phlebotomy needle	€0.634	merkala	*	*
First AUC needle	€1.130	merkala	*	*
Medical gauze	€0.278	merkala	*	*
Cotton pad	€0.062	merkala	*	*
Plastic seal kit	*	*	*	*
Plastic return bag DBS	*	*	*	*
Return envelope	NA	NA	*	*
DBS cards	*	*	*	*
DBS HemaXis kits	€5.000	EO	*	*
Safety lancet	€0.178	doccheckshop	*	*
Vial insert	€0.368	sigmaaldrich	*	*
D200 tip	€0.160	sigmaaldrich	*	*
Ep-tubes	€0.061	sigmaaldrich	*	*
Vials	€0.541	sigmaaldrich	*	*
Caps	€0.301	sigmaaldrich	*	*
Paper sheet	NA	NA	*	*
Big sticker	NA	NA	*	*
Small sticker	NA	NA	*	*
Analysis raegents and isotopes				
Ammonium acetate (g)	€4.828	merck	*	*
Zinc sulfate (g)	€0.099	analytics	*	*
Acetonitril (mL)	€0.200	merck	*	*
Formic acid (mL)	€0.500	sigma	*	*
Methanol (mL)	€0.066	merck	*	*
Sirolimus isotope (10 mg)	€3,250	Alsachim	*	*
Everolimus isotope (10 mg)	€1,850	Alsachim	*	*
Tacrolimus isotope (10 mg)	€7,250	Alsachim	*	*
Ciclosporine isotope (10 mg)	€6,250	Alsachim	*	*
Mycofenolzuur isotope (10 mg)	€4,650	Alsachim	*	*
Energy				
Electricity (kWh)	€ 0.083	[68]	0.523	[69]
Natural gas (m3)	€ 0.355	[68]	1.785	[70]
Heat (GJ)	€ 11.600	[68]	0	[71]
Water (M3)	€ 3.060	[68]	0.780	[68]
Oil (L)	€ 1.340	[68]	2.631	[70]
Other activities				
Waste handling (kg)	€0.100	[55]	1.030	[70]
Special hospital waste (kg)	€1.000	[55]	1.030	[70]
Parcel delivery	€1.92 - €3.84	[59]	0.720	[87]

*: Costs or emissions included within other variable. NA: not taken into account. EO: expert opinion

B Appendix - Environmental impact, CO_2-valued

As mentioned in section 6, the way in which environmental impact is valued has a major impact on overall results. As shown in figure 13, the order of parameters having the most impact on the NMB is changed completely compared to figure 11. Table 9 shows all saved costs, emissions, and NMBs associated with the sensitivity analyses. It also compares NMBs of the analyses to that of the base case. It can be noted that values are further apart compared to the results of NMBs valued with DALYs

Figure 13: Tornado plot of sensitivity analyses in kg CO_2e

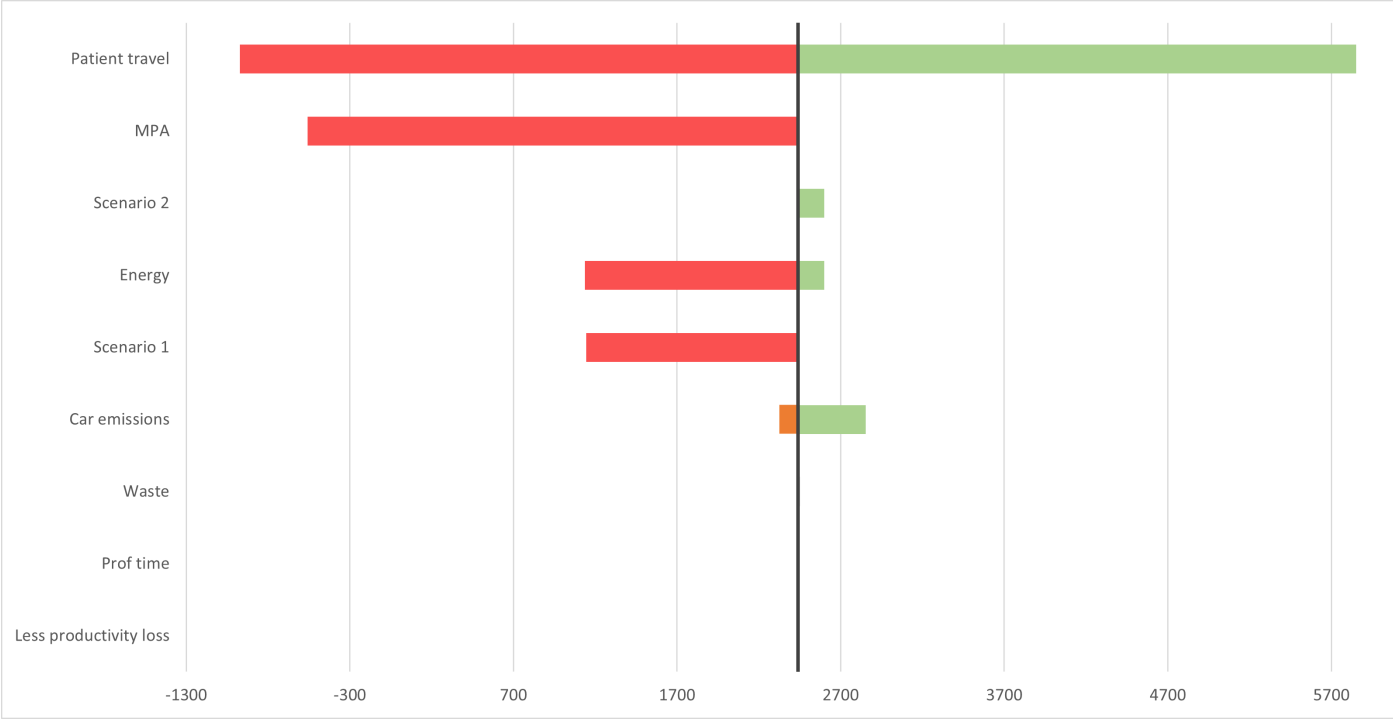

Table 9: Mean costs, emissions and averted DALYs in the PSA

Analysis	Averted kg CO_2e	CO_2e-BC
Base Case	2440	
(1) 0.7 Waste	2429	-11
(1) 1.3 Waste	2450	10
(2) 80% green	1136	-1304
(2) Coal	2601	161
(3) Low emiss	2852	412
(3) High emiss	2324	-116
(4) MPA 0	-559	-2999
(5) No travel DBS	5852	3412
(5) Further DBS	-973	-3413
(6) Less productivity loss	2440	0
(7) No extra PA PH time	2440	0
(7) Extra PA PH time	2440	0
(8) Extra time, 3x kit	1145	-1295
(9) 2x Fuel, coal emissions	2601	161

Emission savings of each sensitivity analysis is compared to the BC. Negative sign means the savings are less compared to the base case. Abbreviations: BC: base case.