RESEARCH ARTICLE

Investigating the health-economic profiles of biomarker-driven immunosuppresion (BIO-DrIM) following solid organ transplantation

Simon Anton Weber[1,2], Malte Pietzsch[2], Oriol Bestard[3], Josep M Grinyo[3], Ondrej Viklicky[4] and Petra Reinke[1,5]

On behalf of all academic and industry members of the EU BIO-DrIM consortium

[1] Berlin-Brandenburg Center for Regenerative Therapies, Charité Universitätsmedizin Berlin, Germany

[2] Cellogic GmbH, Berlin, Germany

[3] IDIBELL, Hospital Universitari de BELLVITGE, Barcelona, Spain

[4] Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[5] Department of Nephrology and internal intensive Care, Charité Universitätsmedizin Berlin, Germany

Abstract: Immunosuppression (IS) following solid organ transplantation is indicated to avoid rejection but puts a significant burden on patients and healthcare systems due to life-long medication dependency and associated costs. Organ-tolerance with low or no IS medication has been observed, and might be forecasted with the help of appropriate biomarkers. Individualized treatments raise the question whether benefits of individualization outweigh the costs of stratification. This article outlines the importance of early economic evaluation in the context of biomarker-guided IS and discusses challenges that an economic evaluation should address, using the BIO-DrIM project as a reference example. We report on design aspects and health-economic study integration into several newly designed biomarker trials. In these studies, health-economic endpoints were defined to measure benefits of individualization and to compare them to the costs associated with stratification. Key economic outcomes to be collected are resource consumption and patient quality of life. Test accuracy of the biomarker-stratification is critical for the clinical success and the health-economic viability of an individualized reduced IS regime. However, IS regimes are not well standardized, rendering comparator choice difficult. The multi-national character of the trials adds further complexity that needs to be addressed. Developers of biomarker tests should stress the importance of integrating health-economic evaluations early into product-development.

Keywords: transplantation, immunosuppression, biomarker, individualized medicine, cost-effectiveness, cost-utility, micro-costing

*Correspondence to: Simon Anton Weber, Berlin-Brandenburg Center for Regenerative Therapies, Charité Universitätsmedizin Berlin, Germany; Email: simon.weber@cellogic.de

Received: November 3, 2015; **Accepted:** January 2, 2016; **Published Online:** March 18, 2016

Citation: Weber S A, Pietzsch M, Bestard O, *et al*. 2016, Investigating the health-economic profiles of biomarker-driven immunosuppresion (BIO-DrIM) following solid organ transplantation. *Advances in Precision Medicine*, vol.1(1): 66–77. http://dx.doi.org/10.18063/APM.2016.01.004.

Introduction

Immunosuppression Following Solid Organ Transplantation

Solid organ transplantation is the treatment of choice for many indications involving organ failure and malfunction. To avoid rejection of the transplanted allografts it is necessary to apply immunosuppressive drugs, typically for the rest of a patient`s lifetime. Life-long immunosuppression (IS) puts a significant burden on patients due to potentially severe medication-related side-effects. At the same time, it puts a significant burden on health-care systems due to high medication costs and costly treatments of side-effects.

Typical current immunosuppressive therapies are not well standardized and consist of a combination of three to four immunosuppressant agents that are combined based on a clinical assessment and on individual weighting of patient-specific risk-factors, including each patient`s ability to metabolize the various IS medications. The patient-specific risk stems from two opposing features of IS medication; under-exposure to IS may lead to rejection episodes, organ damage, and/or graft-loss, while over-treatment involves an increased risk of opportunistic infections (especially EBV, CMV and BKV) and malignancies, as well as drug-specific complications including post-transplant diabetes mellitus, nephrotoxicity and hypertension[1]. In order to find the right balance according to dosing and IS combinations for each patient, therapeutic drug monitoring (TDM) is employed to control blood trough levels of several components of the IS medication[1].

Experience from past clinical trials revealed that the risk for acute rejection episodes is highest during the first three months after transplantation[2]. Therefore, it has been argued that the IS regimen should be highest during this initial period, but should be tapered afterwards to limit severe side effects. As a result, IS medication protocols were refined and can today be separated into an induction and a maintenance phase. No scientific consensus has been reached yet in which patients, at what time, and how fast the tapering of which component of IS medication should be conducted[2–3]. This is particularly striking not only in light of the many undesirable side-effects that limit the overall effectiveness and the patient's adherence to therapy, but importantly also in light of the high cost of IS-induction therapy with Basiliximab or Alemtuzumab. For example, the 2-year costs of four different immunosuppressive strategies, either based on Sirolimus, Cyclosporine, Everolimus or Tacrolimus, have been shown to vary between 26,732 EUR and 49,978 EUR[4].

Organ-tolerance in patients that are effectively on low IS medication or no IS medication at all, has been observed in many patients with various transplanted types of allografts[5–7]. Unfortunately, organ tolerance without IS medication cannot be reliably anticipated to date. Based on these observations, the clinician`s desire to find safe and tolerable strategies to minimize IS following SOT becomes evident.

A clinically feasible solution could be a routine assessment of suitable biomarkers to detect patients who will be tolerant to the allograft with low IS medication or no IS medication at all. Such biomarkers have been discovered, but their routine assessment and the related precision with regard to correct patient stratification and the corresponding health-economic profiles of such strategies have not been studied to-date in prospective RCTs.

Need for Economic Evaluation of Biomarker-guided Reduction of Immunosuppression

Several useful biomarkers were identified in the field of solid organ transplantation throughout the last years[8,9]. They can be grouped into pre- and post-transplant markers indicating either a high risk for rejection or tolerance of patients towards their transplant. In the case of renal transplantation they might even be used to personalize immunosuppression regimes and dosages and to establish success of tolerance-inducing or immunosuppression minimization protocols. The combination of several markers could even further improve the quality of such a test, compared to a single biomarker[6].

Once safe mechanisms for the minimization of IS have been identified and established, there is a strong belief that these strategies would inevitably be cost-effective and even lead to overall monetary savings for respective healthcare systems[3]. However, this is not necessarily the case, especially when pre-transplant stratification is expensive and/or only a small cohort can profit from reduced IS medication. Even if the costs of a routine pre-transplant biomarker test were small, the effects on a patient population in terms of costs for treatments of IS side-effects, rejection episodes and subsequent hospital admissions and outpatient visits can be substantial, justifying the need for quantitative health-economic evaluation[10]. Indeed, pre-

liminary data coming from non-randomized biomarker-driven multi-center pilot studies[11] have shown the feasibility of such studies enabling the identification of such group of transplant patients that may benefit of low immunosuppression with comparable efficacy outcomes as compared to patients receiving high burden immunosuppression.

Many health-economic evaluations have been conducted in the field of IS medication[4,12–14], but to our knowledge there is no health-economic evaluation published to-date about the cost-effectiveness and/or cost-utility of a biomarker-guided (individualized) reduced IS medication plan following solid organ transplantation.

Moreover, the standards for health-economic evaluations are currently not well defined in the field of personalized treatment strategies, as already stated by Hall *et al.*[15]. A fact that may pose a threat for developers due to delayed approval and uptake of care-improving and individualized treatments as well as for patients` health in consequence. The BIO-DrIM consortium in general and this paper in particular seek to contribute to identifying challenges specific to the health-economic evaluation of personalized treatment strategies and present suggestions on how those challenges could be addressed.

The BIO-DrIM consortium is made up of sixteen partners, including clinical institutions, universities, research-performing SMEs, and big-pharma companies. Seven countries are represented: Germany, France, Italy, the United Kingdom, the Netherlands, Czech Republic and Spain. The participating groups have been chosen for their scientific excellence, technical expertise, and experience in translational research. The BIO-DrIM project includes five investigator-driven biomarker clinical trials in the field of kidney and liver transplantation designed by the consortium with more than thousand patients in six EU member states. An important challenge, although not specific for biomarker-evaluation, arises from the multi-national character of the clinical trials: since trial data will come from patients in various healthcare systems with varying reimbursement regulations, a *normalization* strategy will need to be applied to our analyses.

This paper further illustrates the importance of health-economic considerations in evaluating the benefits of future biomarker-driven immunosuppression (BIO-DrIM). Special interest was given to the question, whether or not additional benefits related to a pre- transplantation stratification strategy — e.g. due to increased quality of life (QoL) or less side-effects and post-transplantation costs — outweigh the costs of prospective stratification.

Materials and Methods

Early Health-economic Evaluation

Health-economic evaluations become increasingly important in the field of product development and health technology assessment (HTA) as national healthcare budgets seek to allocate financial resources more and more efficiently. Health-economic evaluations aim to identify treatment-related health outcomes and costs and put both in relation to each other in order to inform policy decisions as well as marketing approval, reimbursement, and other decisions (e.g. internal investment decisions). It is recommended to integrate health-economic considerations into product development decisions at early stages in order to make developers familiar with health-economic benchmarks that need to be met and thereby to continuously reduce the inherent uncertainty throughout the development phase[16]. Another advantage of early integration of health-economics is the ability to provide health-economic data for authorities at early stages and making the authorities familiar with the intervention under consideration. Engaging in early dialogue with payers and regulators proved to be useful from a developer`s perspective[17,18].

Health-economic Decision Problem in the Context of Biomarker-guided IS

The resulting health-economic decision problem of the BIO-DrIM trials can be summarized as outlined in Figure 1. Traditional IS regimen (referred to as “High IS” in our context) based on a clinical assessment, and individual weighting of patient-specific risk-factors represent the standard of care (SoC) and are referred to as comparator. Health-economic outcomes for this strategy will be collected and compared with the outcomes of the innovative biomarker-guided strategy that intends to taper IS for eligible (negatively tested) patients and let other patients (positively tested) remain on standard IS medication (High IS). The selected health-economic outcomes have been defined in close collaboration with clinical scientists and are described in the next section.

Health-economic Endpoints

The assessment of health-outcomes is a complex subject

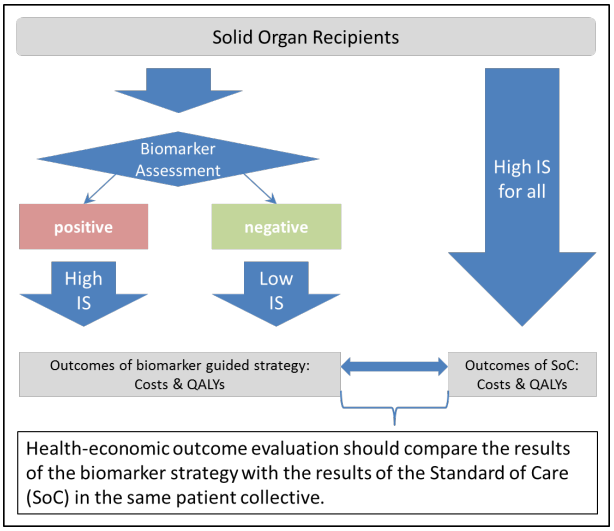

Figure 1. Health-economic decision problem of biomarker-guided IS following SOT. Health-economic outcome evaluation primarily based on costs and QALYs should compare the results of the biomarker-guided strategy with those of standard of care for the same patient cohort. Standard of care represents a high dosing of immunosuppressive medication, while patients receiving the biomarker-guided immunosuppression, will be assessed prior to transplantation and stratified to high (in case of a high risk for rejection) and low IS (in case of a low risk for rejection) accordingly.

as appealingly outlined by Sculpher and Claxton[19]: "Technologies in one disease area (e.g. diabetes) often have impacts on outcomes in other areas (e.g. cardiovascular, wound management, ophthalmology, etc.), each with specific measures of outcome. Therefore, technologies are likely to offer a complex prospect of effects on very many dimensions and measures". The major challenge is to make health outcomes in various dimensions comparable to each other or even across indications. This can be achieved through calculation of Quality-Adjusted Life Years (QALYs).

QALYs take into account both, subjective quality and objective quantity of remaining life years. The remaining QALYs of a patient equal the arithmetic product of life expectancy and a measure of the quality of the remaining life-years. According to the subjective quality of a life-year, a QALY places a respective weight on time in different health states. A year in perfect health is worth 1 and a year of less than perfect health is worth less than 1, with death being considered to equal 0. In clinical practice, QALYs are routinely assessed with the help of standardized questionnaires, like the SF-36v2, EQ-5D and others. Figure 2 shows an exemplary QALY-comparison of two hypothetical treatments, and highlights the QALY gain of an innovative treatment approach. Please refer to Cohen *et al.*[20] for a detailed description of

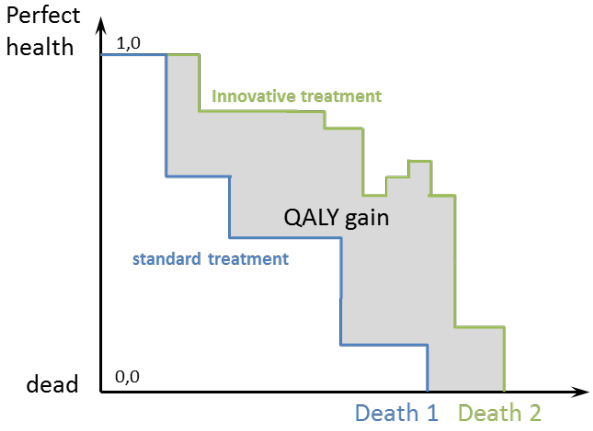

Figure 2. Exemplary QALY gain.

the preference-based QALY concept. The primary health-economic endpoints in all BIO-DrIM trials are QALYs, costs, and costs per QALY per patient at the end of follow-up. These outcome measures are needed for conducting cost-utility analyses. Furthermore, from a health-economic perspective several additional clinical endpoints are important in order to analyze the cost-effectiveness of biomarker guided IS following SOT. Therefore, patient survival (mortality), organ survival (graft-loss), and biopsy-proven acute rejection episodes (BPAR) are assessed in this study and subsequently used in the cost-effectiveness analyses.

Quality of Life — Instruments and Timing of the Assessment

Quality of life (QoL) will be assessed using the generic SF-36v2 and the EQ5D-5L questionnaire, with the latter being used for QALY conversion. The disease-specific Kidney-Transplant-Questionnaire-25 (KTQ-25) will be administered in the case of renal transplantation, and the NIDDK questionnaire in case of liver transplantation in order to capture other disease-related aspects of QoL that cannot be detected by the generic questionnaires, or for which the QALY measure is not sensitive enough. These questionnaires are summarised in Table 1.

The generic EQ5D-5L questionnaire is a widely accepted QoL instrument, and has been recommended by various healthcare payers[17]. It will be administered at baseline (randomization), at Months 1, 3, 6, 12, 18, and 24. Results will be recorded in electronic case report forms (eCRF) and Index-values will be calculated from the answers for each administration. Subsequently, QALY-weights will be obtained using official crosswalk value sets for Spain, UK, France,

Table 1. Quality of life instruments in BIO-DrIM trials

Quality of Life Instruments to be applied in BIO-DrIM Trials		
Questionnaire	**Type**	**Dimensions**
EQ5D-5L	Generic	Mobility, Self-Care, Usual Activities, Pain / Discomfort, Anxiety / Depression
SF-36v2	Generic	Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role, Functioning, Mental health
KTQ-25	Disease-specific	Symptoms related to kidney transplantation and subsequent Immunosuppression
NIDDK	Disease-specific	General, Work, Health, Symptoms, Quality of Life

Czech Republic, Netherlands, and Germany. The mean and median values of accumulated QALYs will be determined for each IS strategy and compared against each other.

The generic SF-36v2 questionnaire is also a widely accepted QoL instrument, and has likewise been recommended by various healthcare payers[17]. It will be administered at the same time-points as the EQ5D-5L and the other QoL questionnaires. Answers will be recorded in an eCRF, evaluated and further transformed according to the official SF-36v2 manual. Scoring of the questionnaire outcomes will be conducted using QualityMetric's Scoring Software v4.5. Scores of each subscale as well as total scores will be compared between treatment arms and between complete treatment-strategies where possible. Specific focus will be given to an exploratory comparison of mean scores of subscales between treatment arms to detect differences in specific aspects of QoL that are not anticipated yet. Furthermore, a mapping of SF-36 results to QALY weights will be performed as cross-check, to ensure a high quality of results with respect to QALYs that will further be used in cost-utility analyses and health-economic modelling[21].

In trials recruiting renal transplant recipients, the disease-specific QoL questionnaire, KTQ-25 by Andreas Laupacis[22], will be administered at the same time points as the other QoL instruments. The KTQ-25 has been validated for various countries, including Spain, the US and others[23–25]. It focuses on symptoms related to the transplantation and immunosuppression context. It will be used to compare the development of various symptoms between treatment arms. This analysis reflects a rather exploratory investigative approach.

In line with most recent health-economic guidelines[26–28], the timing of the QoL assessments has been set according to expected changes in QoL between treatment arms on the one hand and according to practical considerations (assessment at regular study visits) on the other hand. Most frequent adverse events as well as problems related to immunosuppression are likely to occur early during follow-up[2,29]. Therefore we decided to evaluate QoL more often during the first year with a gradual decrease in assessment frequency (at randomization, M1, M3, M6, M12) and less frequently during the second year of follow-up (M18 and M24). In addition to that, we will assess QoL at baseline (randomization) in order to adjust for imbalances at the outset of the trial.

Cost-assessment — Instruments and Timing

The intended cost-assessments within the BIO-DrIM trials will follow the general steps of identification, measurement (counting), valuation, and discounting of resources. The cost-assessment can be separated into two major blocks:

(i) Micro-costing procedure to determine appropriate costs for the biomarker-stratification procedure in specialized laboratories

(ii) Assessment of patient-specific resource consumption, employment status and medical leave periods by using situation-dependent and study-specific questionnaires for patients and study personnel at regular study visits (M3, M6, M12, M18, M24) and in cases of repeated hospitalizations.

The assessed values for resource consumption will be valued with appropriate prices and discounted / inflated to a present value according to health-economic guidelines[26–28]. The results will further be used in subsequent cost-effectiveness and cost-utility analyses.

Micro-costing to Determine Appropriate Costs for Biomarker-stratification Procedure

Micro-costing is a method proved to be useful for determining detailed cost items of healthcare interventions[30]. It involves the identification, measurement, valuation and discounting of resource consumption items. An example of conducting micro-costing procedures in a laboratory environment is provided by Abou-El-Enein *et al*.[31].

Xu *et al.* report that there is currently a lack of standardization in existing health-economic guidelines that could improve "quality and transparency of future studies and enhance comparability and interpretation of findings[30]. However, an appropriate strategy to determine the costs associated with the biomarker-stratification procedures is provided by Fitzgerald *et al.*[32]. The outlined micro-costing strategy focuses on the fact that variability in results is expected for various patients[32]. Therefore, a sub-study was initiated with a subset of the trial participants to conduct the micro-costing procedure and detect potential differences between patients as well as between treatment arms.

In addition to the inter-patient variability, we also expect inter-lab differences in total biomarker-costs between six European study centers. These differences can occur due to varying regulations on best-practice standards, and/or differences in sample processing in the labs of the various countries and by other factors related to national variations in workflow, salary, price-levels, inflation rates, etc.

Since biomarker assessment could be conducted centrally or locally, depending on the specific BIO-DrIM trial, different micro-costing strategies have been proposed to account for the variabilities as described earlier. Whenever a central assessment of biomarkers is planned in a trial (e.g. by a central pathologist to ensure rater-consistency), it is impossible to conduct a sub-study with several labs in several countries, to account for the international variability in results. In order to detect potential inter-patient variability, we will perform structured interviews with the central laboratory personnel during the course of the micro-costing procedure. Whenever a local assessment of the biomarker test is intended, additional inter-lab comparisons will be performed with respect to the micro-costing procedure to identify systematic international variability in results.

Patient-level Cost-assessment of the Treatment Arms

Patient-level cost-assessment tries to capture as much relevant information as possible requiring a justifiable effort for study personnel and focuses on healthcare utilization during the follow-up in the treatment arms[33]. The higher the effort for study personnel and patients to assess specific data elements the higher are the chances for systematically missing values[34]. Therefore, costs will be assessed using specifically designed health-economic questionnaires. The items of the questionnaires have been identified with the help of the principal investigators (PI) and other trial staff in accordance with health-economic guidelines[26, 35–37]. They comprise so-called "big-ticket" items (e.g. dialysis, re-transplantation, costly cancer treatments as a consequence of over-IS, etc.), items of resource consumption that are likely to differ between treatment arms (e.g. frequencies of BPAR, severe infections, malignancies and the respective treatments, frequencies of serious adverse effects of IS, etc.), information about outpatient healthcare utilization, dependency on care-giving, employment status and medical-leave periods (costs for IS regimen as well as concomitant medications will be tracked separately and incurred in the analyses). A summary of the most important cost items to be captured is provided in Table 2.

Table 2. Cost items in BIO-DrIM trials

Cost items to be recorded within BIO-DrIM Trials include but are not limited to:
• Inpatient LOS
• Time spent in each hospital ward (e.g. ICU, surgery, nephrology etc.)
• Major diagnostic assessments (e.g. CT, MRI, etc.)
• Major therapeutic procedures (e.g. Revision surgery, other surgery, chemo-therapy, etc.)
• Treatment of complications (e.g. rejection episodes)
• Post-transplantation diseases (e.g. stroke, myocard infarction, etc.)
• Re-transplantation
• Dialysis
• Outpatient visits incl. reason for visit and applied services
• Employment status
• Medical leave periods
• Dependency on care-giving

Up to three different versions of the questionnaire have been designed to suit various situations in the study context. They are:

- Details of initial hospitalization, including transplantation procedure (to be completed by trial staff using information from patients' medical records at initial discharge)
- Details of repeated hospitalization (to be completed by trial staff using information from patients' medical records, and from interview with the patient, at repeated discharge)
- Details of regular study visits (to be completed by trial staff using information from patients' medical records, and from interview with the patient, at regular study visits)

Details of initial hospitalization cover all relevant inpatient major diagnostic assessments, procedures and respective justifications for those during the initial hospitalization period, including the transplantation

procedure. This assessment is also needed to adjust total patient-specific costs for relevant baseline disparities which are not attributable to the immunosuppression context. The questionnaire on details of repeated hospitalizations was designed to cover inpatient resource consumption in case of major complications, disease-related or not, requiring a repeated stay in the hospital.

The third version of the health-economic questionnaire will be applied in the case of regular study visits. It covers dialysis and post-transplantation diseases, employment status and medical leave and details about potential outpatient healthcare utilization. The timing of the cost-assessment was defined according to practical trial-considerations and major health-economic needs. The assessment of information about resource consumption at the initial discharge of each patient, follows the health-economic need to adjust for baseline disparities, that are not attributable to the IS context. In case of a repeated hospitalization, it is assumed that a major complication occurred. This complication potentially represents another "big-ticket" item and respective information should be recorded. Last but not least, non-troublesome patients should be assessed with regards to their healthcare utilization at regular study visits at M6, M12, M18, and M24.

Results / Discussion

Health-economic Challenges Stemming from IS Context

The BIO-DrIM consortium faces a special situation in the field of health-economics, because the IS strategies under consideration are intended to evaluate *reduced* medication plans. Typically, health-economists are dealing with the evaluation of innovative treatments, add-on treatments, medical devices and other healthcare interventions that are associated with increased expenditures and improved health outcomes at the same time. The resulting decision problem can be summarized as follows: "Is a payer willing to spend the additional amount of *X* monetary units for an additional unit of health (e.g. QALY)?" whereby the necessary monetary amount of *X* is determined by quantitative health-economic assessments. Taking these results into consideration, a fair decision-maker would apply an objective decision rule in the form of an upper boundary for accepting costly innovative treatments. For example, the maximum cost-effectiveness threshold in the UK is £30,000/QALY gained[38], meaning that the decision maker would accept treatments associated with additional maximum costs of £30,000 per QALY gained by the intervention in comparison to the standard of care.

In the context of evaluating biomarker-guided reduced IS medication, chances of ending up in a situation associated with less total costs, but improved health are clearly present. However, the following rationale needs to be adequately addressed in the context of reduced IS medication in order to produce reliable health-economic results. When reduction of IS is indicated by a respective pre-transplant biomarker result, it can only be performed in a controlled fashion in order to assure patient safety. Due to individual patient-specific metabolism of IS medication, therapeutic drug monitoring (TDM) needs to be performed to reach previously defined IS-concentration target-levels in the patient's blood. The assessments of IS medication concentration in blood levels (TDM) is routinely performed during outpatient visits and are less frequently necessary for patients on a standard "High IS" regime, once they reached a stable trough target-level. This fact potentially increases expenditures for those patients on a reduced IS regime, because they will probably need more frequent blood-level checks to reach continuously decreasing IS-concentration target-levels. Although several effects have been identified that might lead to reduced expenditures for patients receiving reduced IS, the outlined argumentation might drive cost results in the opposite direction and it is not clear to-date whether or not reduced IS regimen are really associated with reduced expenditures per se.

We reviewed clinical guidelines[39,40] in the field of IS following renal transplantation and created a plan for expected outpatient visits for blood level concentration measurements. According to this plan, we expect four additional outpatient visits for blood level concentration measurements for patients with reduced IS medication. Table 3 illustrates the timely assessments of CNI blood concentration levels.

Another important aspect in the context of health-economic evaluation of reduced IS regimes, is the appropriate comparator choice. As outlined above, health-economic evaluations compare specific outcomes between competing treatment options. IS regimes are only fairly standardized as already discussed. This renders the correct comparator choice difficult. Since the IS regimes under consideration usually vary even between study-centers of a single country, a unique

Table 3. Expected schedule for CNI blood level trough concentration measurements (suggested minimum amounts according to referenced guidelines & protocols)

month post transplantation	M1																			M2				M3								
week post transplantation	W1			W2				W3				W4								W5				W6	W7	W8	W9	W10	W11	W12		
day post transplantation	2	4	6	8	10	12	14	16	18	20	22	24	26	28	...	30	32	34	36	42												...
suggested clinic frequency*	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x				x	x	x	x	x	x	x						
blod level checks HIGH**	x	x	x	x																												
blood level checks REDUCED***	x	x	x	x												x	x	x	x													

* suggested clinic frequency by Baker *et al*. 2011: "We suggest that uncomplicated patients, as a general rule, may be reviewed progressively less frequently in clinic: 2–3 times weekly for the first month after transplantation; 1–2 times weekly for months 2–3; every 1–2 weeks for months 4–6; every 4–6 weeks for months 6–12; 3–6 monthly thereafter."

** suggested blood level measurement frequency by Kasiske *et al*. 2010: "We recommend measuring CNI blood levels (1B), and suggest measuring at least: every other day during the immediate post-operative period until target levels are reached (2C); whenever there is a change in medication or patient status that may affect blood levels (2C); whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection."

*** expected TAC steady state according to LeGatt: "Time to steady state: Tacrolimus: 2–6 days (at least four doses)"

standard high IS regime has been defined for all BIO-DrIM trials in consent among the participating study centers. Several options of induction and maintenance IS strategies have been intensely discussed among clinicians and a common standard of care was defined.

Health-economic Challenges Stemming from Biomarker-Assessment Context

Test accuracy is a key parameter in determining cost-effectiveness and cost-utility of biomarker-guided IS reduction. Assuming a patient has been tested false-negative, the IS medication would be reduced although the patient belongs to the high risk-group for developing rejection episodes. This would put the patient at an inappropriate risk, with potentially severe consequences for the patient`s health. Also from a health-economic perspective, such a situation would result in higher costs than necessary and poorer health for the patient assuming the patient rejects the allograft. Additional costs stemming from the treatment of rejection episodes induced by the inappropriately reduced IS will need to be accounted for in this case.

Fewer problems are associated with patients being tested false-positive; these patients would receive standard high IS medication although they would be eligible for a reduced medication plan. Clinical results might be less optimal than under a reduced medication regime, due to higher rates of side-effects. However, this treatment currently represents the standard of care and can therefore be regarded as appropriate. As outlined above, health-economic results of individualized treatment strategies are not only influenced by test accuracy of the stratification procedure but also by the size of the resulting patient cohorts. Assuming a test is available that can separate patients into two groups, one for which the status-quo treatment is optimal and another for which a refined treatment is optimal. The overall health-economic profile of an individualized strategy (in comparison to status-quo treatment for all) deteriorates as the size of the beneficial cohort shrinks. This becomes obvious in consideration of the amount of patients with better health outcomes who could compensate the additional costs of stratification.

When evaluating biomarkers for routine clinical applications from a health-economic perspective, it is necessary to assign a certain price to the respective assessment. In order to find an appropriate price, precise estimates about the costs of performing the test need to be considered. As stated above, micro-costing offers an appropriate method for the assessment of costs that are associated with the biomarker assessment. Depending on who will perform the test and where this is performed in a clinical trial setting, complementing approaches can be employed to account for inter-patient, inter-lab, and inter-national variability of micro-costing results. Since the relevant biomarkers will be assessed centrally in BIO-DrIM trials, we will run a micro-costing approach in the central German study lab. In addition to that, we will obtain prices of input factors from as many participating countries as possible to get an impression about how the actual costs of the biomarker-assessment will vary between the affected countries.

Challenges Related to Early Health-economic Evaluation

Health-economic evaluation is recommended to be integrated into the development cycle of innovative treatments and devices already at early stages[16]. This

can be done already as soon as the initial innovation idea has been formulated. By using comparably rough estimates and methods, initial rough estimates about costs and health outcomes can be obtained at very early stages of development. The performed health-economic evaluations can then be subsequently refined throughout the development process with regard to the employed methods and estimates as input factors to the analyses. In doing so, health-economic results are continuously refined, and more reliable results are obtained by reducing the inherent uncertainty related to the results. It is believed that this strategic approach will reduce uncertainty associated with approval and/or reimbursement decisions.

With regard to the BIO-DrIM trials, this approach was chosen as it reflects most recent finding of health-economic guidelines. Although, phase II trials are also part of the consortium, we intend to collect as much health-economic evidence as possible after accounting for the trade-off between effort to be made to obtain certain data and accuracy of results that can be expected.

Health-economic Challenges Stemming from Multi-national Trial Context

Multi-national clinical trials are increasingly employed in various indications. Especially for health-economic evaluations, the multi-national character of a trial raises additional issues. One of them is the appropriate choice of perspective for the analysis[41]. Health-economic evaluations are designed to inform specific stakeholders of the health-care system: reimbursement and approval authorities, hospitals, developers / scientists, patients and several more. Depending on the stakeholder who shall be addressed with an evaluation, various types of costs should be incurred in the analysis (see Table 4). Furthermore, various timeframes for an analysis will be relevant depending on the stakeholder to be addressed: a hospital might be interested in yearly outcomes while an insurance company is interested in outcomes over a life-time horizon. The longer the chosen time-frame and the broader the perspective of an analysis, the more specific the data on costs and health outcomes need to be assessed.

For the BIO-DrIM trials the follow-up period was determined based on clinical considerations focusing on proving improved long-term graft survival without compromising short-term graft survival. The cost-perspective was discussed and defined in close collaboration with clinical scientists and comprises of all direct medical and direct non-medical costs as well as of other big-ticket items, e.g., periods of medical-leave and potential dependency on care giving during the follow-up. The choice of cost items was based on the idea to perform the health-economic analyses from the perspective of the German Statutory Health-Insurance (SHI), justified by the fact that the biggest share of patients will be recruited from three German study centres. Additionally, Germany is often being referred to as a reference market from a developer`s perspective. All economic results will therefore be calculated in EUR and discounted to a present value according to health-economic guidelines[26].

Limitations

BIO-oDrIM will be the first initiative launching biomarker-based randomized clinical trials in almost one thousand patients with the unique intention to ultimately reduce IS medication in suitable patients. However, due to the various challenges that need to be considered from a health-economic perspective and are outlined above, several limitations of the presented study framework need to be kept in mind and addressed during the analysis- and interpretation-phase.

Partly unreliable health-economic results might stem

Table 4. Possible perspectives of economic evaluations and their related costs (adapted from IQWiG[36])

Perspective			Types of costs	Examples	Reimbursement*
Societal perspective	Insurance perspective	Provider perspective	Direct medical costs	Diagnostics, procedures, drugs, wages for physicians and nurses, etc.	yes
			Direct non-medical costs	Maintenance of facilities, wages for administrative staff, supporting services, etc.	yes
			Additional reimbursable costs	Wage compensations, transfer payments to other social insurance schemes, care giver time, etc.	sometimes
			Indirect costs	Productivity losses, reduced tax payments due to incapacity for work and reduced consumption, etc.	no

* typical reimbursement status referring to standard health insurance contracts in affected countries

from the multi-national character of the trials: Different best-practice standards have developed independently in various countries, especially with respect to the treatment of side-effects of IS medication including BPAR. Since we do not expect perfect biomarker-stratification as well as imperfect IS medication, a small amount of patients to reject their organ no matter in which treatment arms. We have to expect that they will be treated differently according to the best-practice in the respective study center, impeding the standardized treatment patterns in the trials and therefore rendering the analysis difficult.

Another problem refers to the cost-assessment of the biomarker stratification process. As we are dealing with central labs throughout the BIO-DrIM trials, we cannot perform inter-lab comparisons. These would have helped in the detection of international variability in biomarker-provision costs. They can occur due to different working procedures in the laboratories under investigation, different wage-levels, and varying costs for other input factors. Therefore we will assess the biomarker-provision prices for Germany and collect those input factors that might be available in other countries for different costs to get a notion of potential variability.

Conclusion

Health-economic profiles of biomarker-guided reduced IS regimen have not been studied to date in connection to prospective randomized controlled clinical trials. It is not clear whether or not individualized reduced IS regimen are associated with less expenditures, due to the expected effects outlined above, justifying the need for comprehensive health-economic analyses as personalized IS treatment options following SOT become available in clinical routine practice. Several challenges from a health-economic perspective have been identified during the course of defining the trials. We outlined how they have been addressed within the BIO-DrIM Trials.

When a reduced immunosuppressive regime is evaluated, it is important to track all associated services to conduct a safe IS weaning protocol. As TDM is extremely relevant in this case, outpatient visits, especially those with TDM focus, should be tracked in clinical biomarker trials. Furthermore, in the context of IS following solid organ transplantation, comparator arms should be clearly defined as standard practice with respect to IS medication is substantially variable between European countries, and even single hospitals. The definition of a common comparator should be consented with all responsible physicians of a trial. Last but not least, test accuracy is not only central for the clinical applicability but also from a health-economic perspective.

Another interesting aspect from the health-economic perspective has been appealingly outlined by Hernandez-Fuentes and Lechler (2010)[6]: Personalized IS regimen that are associated with less toxicity and side-effects would not only cut expenditures for drugs but also increase the lifetime of the transplanted organ and thereby increasing the availability of organs in the general population[3]. Health-economic analyses quantifying this effect from a societal perspective should be conducted in the future to investigate the value to society stemming from an increased availability of donor organs.

In this paper, we exclusively discussed the effects of pre-transplant biomarkers able to detect patient that are likely to be tolerant to the allograft with low levels

Table 5. List of abbreviations

Abbreviation	Definition
BIO-DrIM	Biomarker-Driven personalized Immunosuppression
BKV	Human Polyomavirus
BPAR	Biopsy-proven acute rejection
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CT	Computed Tomography (scan)
EBV	Epstein-Barr-Virus
eCRF	electronic Case Report Form
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IS	Immunosuppression
LoS	Length of Stay
M1, M2, …	Month 1 after inclusion, month 2 after inclusion, …
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
SHI	Statutory Health-Insurance
SoC	Standard of Care
SOT	Solid Organ Transplantation
TDM	Therapeutic Drug Monitoring
W1, W2, …	Week 1 after inclusion, week 2 after inclusion, …

of IS medication. However, post-transplant biomarkers are also available and may be used, e.g. to detect subclinical rejection episodes. In case a rejection is detected, counter-actions before irreversible organ damage has occurred can be taken and thereby enhance patient- and organ-survival. Furthermore, available and validated post-transplant biomarkers to detect sub-clinical rejections would also ease the adoption of IS weaning protocols and enhance the ethical acceptance of those strategies[6]. Health-economic profiles of such strategies have neither been studied to date, justifying the need for respective evaluations.

Table 5 shows a list of abbreviations used.

Conflict of Interest and Funding

No conflict of interest was reported by all authors. This project is supported by the FP7 EU consortium BIO-DrIM.

References

1. Abboudi H and MacPhee I A M, 2012, Individualized immunosuppression in transplant patients: potential role of pharmacogenetics. *Pharmacogenomics and Personalized Medicine*, vol.5: 63–72.
2. Olbricht C J, 2012, Why do we need biomarkers in solid organ transplantation. *Clinica Chimica Acta*, 1310–1311.
3. Baron D, Giral M and Brouard S, 2015, Reconsidering the detection of tolerance to individualize immunosuppression minimization and to improve long-term kidney graft outcomes. *Transplant International*, vol.28: 938–959.
4. Woodroffe R, Yao G L, Meads C, *et al.* 2005, Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. *Health Technology Assessment*, vol.9(21).
5. Haller M and Oberbauer R, 2008, Calcineurin inhibitor minimization, withdrawal and avoidance protocols after kidney transplantation. *Transplant International*, vol.22: 69–77.
6. Hernadez-Fuentes M P and Lechler R I, 2010, A 'biomarker signature' for tolerance in transplantation. *Nature Reviews Nephrology*, vol.6: 606–613.
7. Lerut J and Sanchez-Fueyo A, 2006, An appraisal of tolerance in liver transplantation. *American Journal of Transplantation*, vol.6: 1774–1780.
8. Babel N, Reinke P and Volk H-D, 2009, Lymphocyte markers and prediction of long-term renal allograft acceptance. *Current Opinion in Nephrology and Hypertension*, vol.18: 489–494.
9. Bestard O, Cruzado J M, Ia Franquesa M, *et al.* 2010, Biomarkers in renal transplantation. *Current Opinion in Organ Transplantation*, vol.15: 467–473.
10. Goodacre S and Thokala P, 2015, The economics of cardiac biomarker testing in suspected myocardial infarction. *Clinical Biochemistry*, vol.48: 213–217.
11. Bestard O, Cruzado J M, Lucia M, *et al.* 2013, Prospective assessment of antidonor cellular alloreactivity is a tool for guidance of immunosuppression in kidney transplantation. *Kidney International*, vol.84: 1226–1236.
12. McEwan P, Dixon S, Baboolal K, *et al.* 2006, Evaluation of the cost-effectiveness of sirolimus versus tacrolimus for immunosuppression following renal transplantation in the UK. *Pharmacoeconomics*, vol.24(1): 67–79.
13. Jürgensen J S, Arns W and Hass B, 2010, Cost-effectiveness of immunosuppressive regimens in renal transplant recipients in Germany: a model approach. *European Journal of Health Economics*, vol.11: 15–25.
14. Muduma G, Shaw J, Hart W M, *et al.* 2014, Cost utility analysis of immunosuppressive regimens in adult renal transplant recipients in England and Wales. *Patient Preference and Adherence*, vol.8: 1537–1546.
15. Hall P S and McGabe C, 2013, What evidence is there for the reimbursement of personalised medicine? *Pharmacoeconomics*, vol.31: 181–183.
16. Ijzerman M J and Steuten L M G, 2011, Early assessment of medical technologies to inform product development and market access — a review of methods and applications. *Applied Health Economics & Health Policy*, vol. 9(5): 331–347.
17. Backhouse M E, Wonder M, Hornby A, *et al.* 2011, Early dialogue between the developers of new technologies and pricing and reimbursement agencies: a pilot study. *Value in Health*, vol.14: 608–615.
18. Drummond M, Tarricone R and Torbica A, 2013, Assessing the added value of health technologies: reconciling different perspectives. *Value in Health*, vol.16: S7–S13.
19. Sculpher M and Claxton K, 2010, Sins of omission and obfuscation: IQWiG`s guidelines on economic evaluation. *Health Economics*, vol.19: 1132–1136.
20. Cohen D J and Rexnolds M R, 2008, Interpreting the results of cost-effectiveness studies. *Journal of the American College of Cardiology*, vol.52(25): 2119–2126.
21. Chuang L-H and Whitehead S J, 2011, Mapping for economic evaluation. *British Medical Bulletin*, vol.101: 1–15.
22. Laupacis A, Pus N, Muirhead N, *et al.* 1993, Disease-specific questionnaire for patients with a renal transplant. *Nephron*, vol.64: 226–231.
23. Rebollo P, Ortega F, Ortega T, *et al.* 2003, Spanish validation of the "Kidney Transplant Questionnaire": a use-

ful instrument for assessing health-related quality of life in kidney transplant patients. *Health and Quality of Life Outcomes*, vol.1: 56.

24. Rostami Z, Tavallaii S A, Jahani Y, *et al.* 2011, Assessment of quality of life in a single-center transplantation population using the Kidney Transplant Questionnaire-25 questionnaire. *Transplantation Proceedings*, vol.43: 590–591.
25. Chisholm-Burns M A, Erickson S R, Spivey C A *et al*. 2011, Concurrent validity of kidney transplant questionnaire in US renal transplant recipients. *Patient Preference and Adherence*, vol.5: 517–522.
26. Ramsey S, Willke R, Glick H, *et al*. 2015, Cost-effectiveness analysis alongside clinical trials II — an ISPOR good research practices task force report. *Value in Health*, vol.18: 161–172.
27. Husereau D, Drummond M, Petrou S, *et al.* 2013, Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMC Medicine*, vol.11: 80.
28. Petrou S and Gray A, 2011, Economic evaluation alongside randomized controlled trials: design, conduct, analysis, and reporting. *British Medical Journal*, vol.342: d1548.
29. Fiebiger W, Mitterbauer C and Oberbauer R, 2004, Health-related quality of life outcomes after kidney transplantation. *Health and Quality of Life Outcomes*, vol.2: 2.
30. Xu X, Nardini H K G and Ruger J P, 2014, Micro-costing studies in the health and medical literature: protocol for a systematic review. *Systematic Reviews*, vol.3(47).
31. Abou-El-Enein M, Römhild A, Kaiser D, *et al.* 2013, Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs. *Cytotherapy*, vol.15: 362–383.
32. Fitzgerald P, Goodacre S W, Cross E, *et al*. 2011, Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the Randomized Assessment of Treatment Using Panel Assay of Cardiac markers (RATPAC) trial. *Society for Academic Emergency Medicine*, vol.18(5): 488–495.
33. O`Sullivan A K, Thompson D and Drummond M, 2005, Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations? *Value in Health*, vol.8(1): 67–79.
34. Dziura J D, Post L A, Zhao Q, *et al.* 2013, Strategies for dealing with missing data in clinical trials: from design to analysis. *Yale Journal of Biology and Medicine*, vol.86: 343–358.
35. Miners A, 2008, Estimating costs for cost-effectiveness analysis. *Pharmacoeconomics*, vol.26(9): 745–751.
36. Institute for Quality and Efficiency in Health Care (IQWiG), 2009, *Working paper — cost estimation*, version 1.0, accessed March 5, 2015, <https://www.iqwig.de/download/Working_Paper_Cost_Estimation.pdf>
37. Shi L, Hodges M, Drummond M, *et al.* 2010, Good research practices for measuring drug costs in cost-effectiveness analyses: an international perspective: the ISPOR drug cost task force report — part VI. *Value in Health*, vol.13: 28–33.
38. The University of York — Centre for Health Economics, 2015, *NICE Threshold Press release*, accessed February 21, 2015, <https://www.york.ac.uk/media/che/documents/NICE%20Threshold%20Press%20Release%20190215.pdf>
39. Kasiske B L, Zeier G M, Chapman J R, *et al.* 2010, KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney International*, vol.77: 299–311.
40. Baker R, Jardine A and Andrews P, 2011, *Post-operative care of the kidney transplant recipient*, 5th edition Final Version, The Renal Association, accessed February 5, 2011, <http://www.renal.org/guidelines/modules/post-operative-care-of-the-kidney-transplant-recipient#sthash.xF6IVBpt.0fbuDlnx.dpbs>
41. Rivero-Arias O and Gray A, 2010, The multinational nature of cost-effectiveness analyses alongside multinational clinical trials. *Value in Health*, vol.13(1): 34–41.