A framework for economic evaluation of therapeutic drug monitoring—guided dosing in oncology

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Abstract
The standard approach for dose individualization of chemotherapy in the oncology setting has long been based on body surface area (BSA) as a measure of body size. However, for many anticancer drugs, administration of dosages based on BSA may result in some patients receiving supratherapeutic or subtherapeutic concentrations due to substantial interindividual pharmacokinetic variability. Therapeutic drug monitoring (TDM)—guided dosing aims to ensure that the patient’s serum drug concentration is in a target range which has been shown to produce optimal clinical outcomes. The management of several malignancies is now moving away from using traditional intravenous chemotherapy to longer-term treatment with targeted molecular therapies. These targeted anticancer drugs are currently dosed based on a fixed dose for all patients. The pharmacokinetic characteristics of most of these drugs (e.g., tyrosine-kinase inhibitors) support implementation of individualized dosing via TDM. However, prior to adopting TDM–guided dosing in oncology settings, the economic efficiency and value for money of introducing TDM interventions should be critically and systematically examined along with the impacts on patient care and outcomes. Yet, current evidence in this area is limited, and more generally, there is lack of methodological guidance on how to identify, estimate and value clinical and cost information necessary to conduct economic evaluations of TDM interventions. In this paper, we propose a coherent framework for conducting economic evaluation of TDM interventions in oncology settings and discuss some practical challenges of conducting economic evaluations of TDM.

KEYWORDS
cost-effectiveness, economic evaluation, oncology, therapeutic drug monitoring
intravenous chemotherapy to longer-term treatment with targeted molecular therapies. These newer therapies are dosed using a fixed dose for all patients. The possibility of estimating the steady-state exposure of older chemotherapy and newer oral drugs creates an opportunity to shift the paradigm from BSA and fixed dose–based dosing to a therapeutic drug monitoring (TDM)–guided dosing.\textsuperscript{1–3} TDM–guided dosing is the process of individualizing dosing through measuring and interpreting systemic drug concentrations in biologic fluids.\textsuperscript{4} For TDM intervention to be clinically relevant, it has to fulfill several drug, disease state and patient-related criteria.\textsuperscript{5} Drugs that are considered best candidates for TDM interventions are those with a narrow therapeutic index (i.e., drugs where small fluctuations in blood concentration may result in life-threatening adverse drug events and/or poor efficacy), high interpatient pharmacokinetic (PK) variability, high cost, and those having well-defined and consistent exposure–response relationships. Many cancers are treated with drugs that meet most of the above drug-related criteria for TDM intervention.\textsuperscript{6–8} For instance, the high variability in drug exposure for most oral targeted therapies such as tyrosine-kinase inhibitors (TKIs), caused by substantial interindividual pharmacokinetic variability, suggest individualized dosing. Recent studies have shown that TDM is feasible for optimizing treatment of some TKIs including imatinib\textsuperscript{9} and sunitinib.\textsuperscript{10}

Considering TDM improves overall efficacy and/or reduces the toxicity of cancer treatments, the high drug acquisition costs of targeted anticancer drugs used for TDM would presumably make TDM–guided dosing cost-effective and represent benefit for public health systems. Yet, current evidence in this area is limited, and more generally, there is lack of methodological guidance on how to identify, estimate and value clinical, and cost information necessary to conduct economic evaluations of TDM interventions. In this paper, we propose a coherent framework for conducting economic evaluation of TDM interventions in oncology settings and discuss some practical challenges of conducting economic evaluations of TDM. The framework can also be utilized as a template to conduct economic evaluations of TDM interventions for medical conditions outside of oncology. The framework provided herein was informed by (i) a comprehensive review of economic evaluations of TDM interventions for cancer treatments,\textsuperscript{11} and (ii) review of reporting guidelines regarding how to conduct an economic evaluation of healthcare interventions.\textsuperscript{12–14}

2 | A FRAMEWORK FOR CONDUCTING ECONOMIC EVALUATIONS OF TDM INTERVENTIONS

The overarching aim of conducting any health economic evaluations is to provide evidence on economic efficiency of an intervention to decision makers with the aim of maximizing the benefits from healthcare spending. As such, a well conducted economic evaluation considers all factors and variables that in one way or another influences/informs the decision to be made (i.e., reject or fund the healthcare intervention). These variables include appropriately formulating the study frame (e.g., clearly stating the perspective(s), intervention and comparator(s), setting and patient population of interest, and time horizon(s) of the analysis), identifying, measuring and valuing health outcomes and resource use, identifying appropriate method of analysis with due consideration given to uncertainty, and summarizing and interpreting the findings.\textsuperscript{12–14}

In the context of precision dosing in oncology, the healthcare intervention and comparator are clear: the intervention is a TDM-guided dosing or TDM and the comparator is that the drug continues to be administered based on a simplified fixed-dosing or BSA approach. The population of interest are patients diagnosed with cancer and are currently on one or more of anticancer drugs eligible for TDM interventions. For economic evaluations alongside clinical trials, it is recommended that only costs and effects that accumulate within the trial period be included in the analysis.\textsuperscript{13} These are relatively short-term costs and effects; however, in some circumstances it may be appropriate to extrapolate or model the longer-term costs and effects. For example, cancer patients who are continually underdosed might have greater likelihood of disease progression and reduced survival.

3 | MEASURING THE IMPACT ON HEALTH OUTCOMES

Depending on the type of economic evaluation (e.g., cost-minimization, cost-effectiveness, or cost-utility analysis), the primary outputs of the analysis can include total direct costs, life years, quality adjusted life-years (QALYs), and ICER. The types of evidence that are relevant for estimating clinical effectiveness (and informing cost-effectiveness analysis) of TDM–guided dosing are those that compare overall survival, progression-free survival, therapeutic response, health-related quality of life (HRQOL), and incidence of adverse drug events (ADEs) between patients randomized to TDM–guided dosing versus fixed dose or BSA-based dosing (Table 1). These outcomes can be collected at baseline and in each follow-up period using structured questionnaires, checklists, or grading tools such as the response evaluation criteria in solid tumors (RECIST 1.1) criteria\textsuperscript{15} for assessing therapeutic response, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)\textsuperscript{16} for grading ADEs, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)\textsuperscript{17} for assessing HRQOL. Individual patient data regarding chemotherapy-related ADEs (e.g., incidence, severity and counts per unit time, and resource use) needs to be collected, and appropriately valued as some of the ADEs are fatal and require an onerous, resource-intensive, and expensive clinical management. ADEs could also lead to poor adherence to therapy, resulting in reduced effectiveness of treatment. The NCI CTCAE utilizes abnormal laboratory findings and/or clinical symptoms to grade ADEs severity into minor (grades 1 and 2) and severe (grades 3 and 4).

Given the high incidence and severity of ADEs among cancer patients taking chemotherapy, and its potential to have a material
Table 1: Overview of health outcomes that are relevant for conducting economic evaluation of TDM-guided dosing interventions

| Health outcome                                         | Means of collection (examples)                                | Timing of collection                              | Source of data          |
|--------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------|-------------------------|
| Overall survival                                       | Period between the date of the start of treatment and the date of death | Throughout the trial period                      | Clinical trial data     |
| Progression-free survival                              | Period between the date of the start of treatment and the date of clinically and/or radiologically confirmed progression | Throughout the trial period                      | Clinical trial data     |
| Therapeutic response                                   | Response rate according to RECIST 1.1 criteria (partial response, stable disease, progressive disease) | Baseline prior to randomization, and in each follow-up periods | Clinical trial data     |
| Adverse drug events                                    | Number and severity of events assessed using NCI CTC criteria | Throughout the trial period                      | Clinical trial data     |
| Health-related quality of life and utility values      | EORTC QLQ-C30 administered via self-report questionnaire     | Baseline prior to randomization, in each follow-up periods | Patient-reported outcomes |

Despite the overall cost-effectiveness estimates, it is crucial that the cost and QALY impacts of ADEs be included in economic evaluations.

Although the choice of the most appropriate type of analysis relies largely on how the interventions compared affect the patients' health state, cost-utility analysis (CUA) is generally the preferred form of economic evaluation in many countries, particularly when (i) the intervention has a meaningful impact on the patient's HRQOL and where appropriate health state utility data have been collected; and (ii) there are multiple patient-relevant clinical outcome parameters expressed in different units. For a CUA, costs are expressed in monetary units and effects in QALYs gained. QALYs are derived by weighting overall survival estimates by utility values representing preferences for health states. Generally, utility values can be obtained using a generic utility instrument, or by mapping disease-specific quality of life data to generic utility measures such as the EQ-5D. The EORTC QLQ-C30 is one of the most commonly utilized disease-specific HRQOL measures in cancer clinical trials worldwide. However, since the EORTC QLQ-C30 is not a preference-based measure, the responses cannot be used in CUA and thus should be mapped to generic utility measures. To make the EORTC QLQ-C30 applicable for CUA, a cancer-specific multi-attribute utility instrument, the QUIC, was derived from the EORTC QLQ-C30 and has been included in the EORTC assessment system. The QLQ-10D includes 10 of the EORTC QLQ-C30’s 15 domains (mobility, role functioning, social functioning, emotional functioning, pain, fatigue, sleep, appetite, nausea, and bowel problems), and captures symptoms and functioning aspects specific to cancer patients.

A cost-effectiveness analysis (CEA) with the outcomes expressed in terms of life-years gained (or other relevant patient outcome) can be carried out in situations where (i) there is a clinically significant effect but lack sufficient information to perform CUA; (ii) the QoL instrument used is not sensitive to changes in patient’s health state; or (iii) if improving life expectancy is the main objective of the intervention. In the context of TDM intervention where the main objective is to avoid therapeutic failure and/or reduce toxicity, outcomes can be expressed in terms of (i) the cost per ADEs averted, and/or (ii) the cost per person underdosed (failing to receive an optimal dose) averted.

In addition to measuring and valuing the outcomes that result from implementing a TDM-guided dosing intervention, it is important to identify, estimate and value the costs of resources consumed in the process of developing, implementing, operating, and delivering the TDM intervention. A bottom up, micro-costing approach, the most accurate, and precise costing method, should be utilized to obtain reliable data for estimating intervention costs. The first step in micro-costing is to identify the tasks involved in a trial (i.e., inputs), and the resources needed for each task. Each input will then be enumerated and assigned a unit cost value and aggregated to derive the total cost.

In the context of TDM interventions, resources used for activities involved in all steps of TDM monitoring should be considered, along with total drug costs (chemotherapy and other drug), costs of ADEs, and others (e.g., non-hospital costs). Ideally, the trial investigator(s) should track resource use and collect all cost data during the trial period. This can be done either: (i) prospectively via direct observation of the intervention processes or using activity logs to record the resources used, or (ii) retrospectively using standardized comprehensive templates, targeted questionnaires, or retrospective examination of records. Table 2 summarizes an overview of the resource use and cost measures for conducting economic evaluation of TDM-guided dosing interventions. An overview of the resource use and cost measures for conducting economic evaluation of TDM-guided dosing interventions in an Australian setting is also provided as a File S1.

4.1 TDM costs

Although most drug levels are sent to a commercial central laboratory for assay, TDM can also be performed within an appropriately accredited clinical pharmacology laboratory such as those designed for clinical trial purposes. For TDM conducted by a commercial laboratory, the cost per completed TDM assay can easily be taken from the official company price. In the latter case,
the cost of TDM for one assay can be calculated by adding the equipment costs (e.g., reagents and consumables such as glassware, columns, tubes, eluents, and quality control samples) to the total operating costs (e.g., staff costs such as the time spent by the physician, nurse, laboratory technician, and pharmacist) associated with one assay. The costs of fixed resource use (i.e., the cost of TDM laboratory space or facility, and equipment such as liquid chromatography–tandem mass spectrometry) should also be taken into consideration. When calculating fixed costs associated with a TDM service, it is important to keep in mind that the TDM laboratory, as with many other laboratories, has several types of equipment that are not directly related to PK testing but are vital for day-to-day running of the service, each with different life expectancies. Therefore, it is necessary to apply relevant depreciation rates (e.g., 20%) for all relevant laboratory equipment over its useful lifetime. The costs of TDM services per patient can then be calculated by multiplying cost of providing TDM service for one assay by the number of assays performed for the patient. The number of TDM assays needed per patient, in turn, depend on the number of dose adjustments required for the specific patient and is largely informed by various clinical parameters (e.g., the occurrence of unexpected toxicity after initial stabilization of dose) and/or expert opinion.

4.2 | Staff costs

Time spent by staff implementing TDM intervention represents key resource use and should be considered when calculating the cost per completed TDM assay. This includes staff costs incurred obtaining a blood sample (based on time spent by health visitor with the patient or at an outpatient appointment) and laboratory staff timings (i.e., sample receipt and preparation, HPLC determination with column switching, quality control run, calibration, and documentation of data). Formulating dosing advice involves not only interpretation of TDM results, but also a clinical assessment of patient conditions. Thus, the time spent by the pharmacist or clinical pharmacologist interpreting and reporting TDM results, and dose recommendations, and the clinician evaluating patient conditions and monitoring the patient following dose adjustments should also be included in economic evaluation. Once the trial is well underway, an activity log such as a time log that covers an entire day can be used to record (preferably on the same day) the time spent by each staff implementing the intervention. Once the number of hours spent by staff are properly measured, an appropriate hourly rate (depending on depends on the skills and trainings of the staff) can be applied to estimate staff cost.

4.3 | Drug costs

The overall cost of chemotherapy is estimated based on dose, cycle, and duration of therapy. For the non-TDM-guided dosing, each patient receives either receives a standard fixed dose or mean body surface area (BSA) is used to calculate the dose needed for the patient, whereas for the TDM-guided dosing, the drug cost is estimated for each patient based on the final dose recommendation from TDM since some patients might receive more and some patients receive less dose. The average cost for a unit of each drug is then applied based on the current pharmaceutical schedule; in Australia, drug costs from the Pharmaceutical Benefits Scheme (PBS) are commonly used for drugs dispensed in the community. Costs of laboratory and clinical investigations, and costs associated with the administration of first dose (if applicable) are common to both intervention and usual care.

4.4 | Costs of adverse drug events

The costs of ADEs can be calculated based on the proportion of ADEs requiring hospitalization and can be costed as either an inpatient episode or as a prescribed drug therapy (i.e., IV antiemetics). For costs associated with ADEs most likely to result in hospitalization (i.e., grade 3 or 4 ADEs such as febrile neutropenia), the cost of hospitalizations and emergency department visits (e.g., physician fee, and hospital reimbursement) should be included. Although the costs of grade 1 and 2 ADEs are generally considered to be low, it is important to document and include any resource use associated with the management of these ADEs. Depending on the study perspective (e.g., societal perspective), costs such as the cost of a hospital stay (i.e., room charges and non-medical services such as transport and/or parking) might also be considered; however, these costs might swamp the cost of TDM intervention.
4.5 | Economic analysis of the data

Once all costs and outcomes are identified and appropriately valued, incremental cost-effectiveness ratio (ICER) can be calculated by dividing the difference in cost of intervention (i.e., TDM-guided dosing) and comparator (i.e., BSA-based or fixed dosing) by the difference in their effects. Some of the analysis features that are common to any trial-based economic evaluations include the use of intention-to-treat population for the primary analysis, a within-trial assessment of costs and outcomes (regardless of plans to extrapolate costs and outcomes beyond the time horizon), the use of discount rate for future costs and outcomes, and assessment of uncertainty.

Ideally, for a trial-based CUA to be relevant for reimbursement decision-making, the analysis need to include the full range of alternative options, relate to the population that will receive the interventions being evaluated, and have a follow-up period consistent with the appropriate time horizon. However, in practice, it is difficult to design a CUA that fulfill all these criteria, and modelling is often used to deal with some of these design issues (e.g., modelling can be used to extrapolate short-term cost and utility data from RCTs over a longer time horizon).

When calculating ICER of TDM intervention in oncology setting, it is important to keep in mind that the cost and effect data may vary according to type and severity of cancer (e.g., early vs. late stage), leading to differences ICERs with potential implications for reimbursement. In such cases where the overall ICER for TDM intervention is likely to fall below the acceptable threshold, but when there might be subgroups who might gain greater benefit from precision dosing, it is important to calculate ICER in these subgroups of patients. It may also be helpful to apply modelling and use multiple sources of evidence in such circumstances where heterogeneity in baseline disease states can drive important differences in ICER. For a detailed discussion on how to conduct trial-based CUA, readers can refer to The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices Task Force Report on cost-effectiveness analysis alongside clinical trials.13

5 | DISCUSSION

Although findings from recent clinical trials of oral targeted therapies such as TKIs support implementation of precision dosing via TDM, the feasibility and clinical utility of adopting TDM-guided dosing in routine practice is yet to be explored. Prior to adopting TDM interventions in routine clinical practice, the additional cost and resource utilization associated with it should also be justified against its overall benefit to the patient, providers, and health system. Considering the high acquisition cost of recent targeted anticancer agents such as Imatinib, implementing a TDM intervention (if proven effective in improving patient outcomes) may represent good value for money. However, the scarcity of good quality clinical evidence and cost information in this area make it difficult to evaluate the economic outcomes of TDM interventions in this population. In Australia, a research program called Pathway of Research to Evaluation of Dose-Individualised Cancer Therapy (PREDICT) has been recently funded by Cancer Council NSW to develop a national individualized cancer-dosing program to generate evidence and implement existing evidence on algorithms for dosing targeted and non-targeted chemotherapy.25 Research protocols have already been completed for TDM-guided dosing for SFU and selected TKIs. Findings from these prospective clinical studies will generate clinical and cost information necessary to develop and implement high quality PK-based decision support for real world clinical dosing of a range of old and new anticancer drugs.

While clinical and resource use data from RCTs are now commonly utilized to examine cost-effectiveness of healthcare interventions,26 RCTs do not always provide sufficient cost and/or clinical data relevant for informing funding decisions, and do not run for long enough time to capture differences in clinical and economic outcomes between comparators.26 For instance, while the costs of TDM interventions are incurred during the trial period, some of the outcomes of TDM-guided dosing (e.g., survival) may not be apparent during this period, potentially leading to inaccurate conclusions. In such circumstances, extrapolating short-term evidence from RCTs (including costs and utilities) over a longer time horizon may be warranted. However, due to the absence of methodological guidance for extrapolation of non-time to event outcomes and degree of uncertainty surrounding the validity of assumptions, healthcare decisions made based on extrapolated evidence are often disputed. Alternatively, decision analytical modelling can be utilized to simulate progression, mortality, and resource use of fixed, BSA-based dosing versus TDM-guided dosing over a lifetime or a certain period. In addition to the possibility of extrapolating beyond the data observed in RCTs, decision-analytical models offer the opportunity to link intermediate clinical endpoints to final outcomes and inform decisions in the absence of hard data. In fact, the majority of published economic evaluations of TDM-guided dosing in oncology setting employed Markov models, partitioned survival model or decision-trees.11 The major limitation of these studies (and more broadly use of economic models for TDM interventions), however, is that they relied on lower quality clinical evidence (e.g., retrospective cohort studies, patient records) as there is a scarcity of good quality RCTs of TDM interventions with appropriate comparators in oncology setting.11

In summary, the economic efficiency and value for money of introducing TDM interventions in oncology settings should be critically and systematically examined along with its impacts on patient care and outcomes. Future RCTs should be designed and conducted in a way that will enable researchers to collect data on resource use and health outcomes that are relevant for conducting cost-effectiveness analysis.

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All authors declare that there is no actual or potential conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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