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A comprehensive review of economic evaluations of therapeutic drug monitoring interventions for cancer treatments

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Abstract

Therapeutic drug monitoring (TDM) of cancer drugs has been shown to improve treatment effectiveness and safety. The aim of this paper was to comprehensively review economic evaluations of TDM interventions for cancer drugs. Searches were conducted in four electronic databases, Medline, EMBASE, and Centre for Reviews and Dissemination (CRD) databases' Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (NHS EED), from their inception to June 2019. Studies were included if they were economic evaluations of TDM interventions for an active cancer treatment. The quality of reporting of economic evaluations was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS checklist). Of the 11 publications identified, imatinib with TDM and 5-fluorouracil (5-FU) with TDM were the most commonly assessed interventions (4 publications each). Overall Study quality was good, with publications meeting 61% to 91% (median 80%) of CHEERS checklist criteria. A variety of studies were used to estimate the clinical effectiveness inputs for the cost effectiveness models. All publications considered TDM to be cost-effective based on an ICER below the WTP threshold (64%) or being cost-saving (36%). TDM interventions were considered cost-effective across the economic evaluations. Further clinical research assessing the impact of TDM on overall survival or other long-term health outcomes may enhance the evidence base for TDM in oncology. Future economic evaluations of TDM should explicitly consider uncertainty in the underlying clinical evidence and incorporate changes in the use of newer targeted drugs that form the current standard of care.

Keywords: therapeutic drug monitoring, cost-effectiveness, cancer, imatinib, fluorouracil

Introduction

There is a strong rationale for the use of therapeutic drug monitoring (TDM) in oncology. Many 'traditional' anticancer drugs have substantial inter-individual pharmacokinetic variability with existing dosing regimens, steep dose-response curves, and narrow therapeutic windows; resulting in serious toxicity from overexposure and insufficient response from underexposure [1, 2]. Additionally, newer targeted treatments such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies have also demonstrated substantial pharmacokinetic variability [3]. Where a concentration–effect relationships has been established, TDM provides an opportunity to tailor treatment to minimise toxicity and prevent undertreatment [1, 2].

There is strong clinical evidence supporting TDM for several anticancer drugs. Randomised trials have demonstrated improvements in clinically meaningful outcomes such as reductions in grade 3 and 4 AEs associated with 5-FU [4]and higher rates of major molecular response (MMR) in chronic myeloid leukaemia (CML) [5]. However, uptake of TDM for cancer treatments has been limited to a small number of agents [6]. Reasons for the limited uptake include difficulty establishing target drug concentrations and logistic challenges. Additionally, the intermittent, cyclic administration of many anticancer agents prevent dose adjustment until the subsequent treatment cycle during which patients may experience severe adverse events (AEs) that TDM help prevent [2].

The clinical benefits of TDM are likely to translate to meaningful economic outcomes that may provide further impetus to implement TDM in oncology practice. We aimed to comprehensively review economic evaluations of TDM interventions for active cancer treatments. This review was performed as a part of the Pathway of Research to Evaluation of Dose-Individualised Cancer Therapy (PREDICT) Program which aims to develop a

personalised chemotherapy dosing system for cancer patients to improve quality of life, reduce side effects and increase chance of survival [7-9]. Findings from this review will inform development of economic evaluations of TDM interventions for cancer treatment.

Methods

The literature search aimed to identify economic evaluations of TDM interventions for active cancer treatments. The Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) strategy was followed to ensure systematic selection of studies [10]. The PRISMA checklist is presented in Table 1.

Electronic searches

Electronic databases Medline, EMBASE, and Centre for Reviews and Dissemination (CRD) databases' Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (NHS EED) were searched from inception to current on 21 June 2019. Updates to the DARE and NHS EED databases ceased in March 2015 and searches of databases ended in December 2014 [11]. Medical Subject Headings (MeSH) and keywords related to cancer, drug monitoring, economic evaluation, and a comprehensive list of antineoplastic drugs [12] were used for the searches of Medline and EMBASE. The keywords 'therapeutic drug monitoring' and 'drug monitoring' were used to search the CRD databases. The full search strategies are provided in Supplementary Material Appendices 1–3.

Study selection

Studies were included if they examined a TDM intervention for an active cancer drug and included an economic evaluation. Studies that compared a TDM treatment regimen with a different drug regimen were excluded as they were primarily assessing two different treatment strategies rather than a TDM intervention. Economic evaluations of TDM interventions for supportive cancer treatments (e.g. antimicrobials) were excluded as were

non-English studies. Both full-text publications (referred to as 'articles') and abstracts were included as one abstract used RCT data [13] and another abstract better reflected modern standard of care[14]. Compared with the full-text publications, the abstract publications, with the exception of one[14], were more contemporaneous and published after 2017[13, 15-17].

Two reviewers (DV and AM) independently screened the titles and abstracts, followed by full-text publications of the identified citations according to exclusion and inclusion criteria. Disagreements between reviewers were resolved by consensus.

Data extraction

A data collection table was developed and refined based on the publications. One reviewer (DV) extracted the data on study characteristics and information about the economic evaluation. A second reviewer (AM) reviewed the extracted data of a random sample of the included studies (five studies, six economic evaluations). Data extracted from the included publications included key characteristics of the economic evaluation, rationale for modelling choices (type of economic analysis and model, perspective, time horizon and discount rate), clinical effectiveness data, utility values, extrapolation methods, results (outcomes, intervention costs, ICERs, costs of the TDM intervention, and components of TDM intervention included in the costs), study limitations, funding and potential for conflicts of interest. Additional data on clinical effectiveness and utility values were sourced from referenced publications. We endeavoured to extract the same data from both full-text publication and abstracts, however it was expected that the abstracts provide limited details. Costs and ICERs were converted to 2018 United States dollars using the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) calculator which converts costs using Gross Domestic Product (GDP) deflator index and Purchasing Power Parities for

GDP data from the Organisation for Economic Co-operation and Development (OECD) [18, 19].

Assessment of the quality of reporting of studies

The quality of reporting full-text publications were assessed by one reviewer (DV) using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS checklist) by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[20]. The CHEERS checklist can be used to assess the quality of reporting of economic evaluations. It consists of 24 items that are dichotomously assessed as having met the criterion or not (Yes or No). CHEERS checklist items that were not fully met were assigned a 'No'. Study quality for the publications that presented more than one analysis was assessed for each analysis.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

The search identified 3,289 unique publications of which 60 publications underwent full-text review and 11 publications, consisting of six articles and five abstracts, were included (Figure 1). Compared to the full-text publications, the abstracts were more recently published.

The six articles presented eight economic analyses due to two publications presenting two economic analyses. An overview of the economic evaluations is presented in Table 2. Nine cost utility analyses were presented across eight publications [13-16, 21-24]. Cost analyses were presented in 2 publications [25, 26]. Cost effectiveness analyses were presented in a

total of three publications [17], including two that were presented alongside trial-based cost utility analyses [23, 24].

Three of the five abstracts[13, 15, 16] presented cost-utility analyses on imatinib for CML, while the other two presented economic evaluations on 5-FU TDM for colorectal cancer[14] and pancreatic cancer[17].

One study[27] was not strictly a TDM paper as it assessed conventional weight-based dosing regimens with alternative pharmacokinetic-based regimens. The pharmacokinetic-based regimens achieved an exposure (area under the curve) and target engagement (or receptor occupancy) similar to that of a 'typical' 75 kg patient. The resulting pharmacokinetic-based regimens used revised dose based on patients' body weight rather than individual dose adjustment based on concentration–effect relationships used in TDM. However, this study was included as the pharmacokinetic-based regimens were based on pharmacokinetic and pharmacodynamic relationships to optimised the dosage of high cost cancer treatments is of topical importance[28, 29].

Cancers

Colorectal cancer [14, 22, 24] and chronic myeloid leukaemia [13, 15, 16] (3 publications each) were the most common cancers that were the focus of TDM interventions (Table 3). The remaining publications analysed TDM interventions for breast cancer [21], head and neck cancer [22], gastrointestinal stromal tumour [23], acute lymphoblastic leukemia[26], and pancreatic cancer[17]. One publication assessed hypothetical pharmacokinetic dosing regimens for two treatments for melanoma[27].

Interventions

A summary of the TDM interventions assessed in the economic evaluations is presented in Table 3. Imatinib TDM [23] [13, 15, 16] and TDM of 5-fluorouracil (5-FU) [14, 17, 22, 24]

were assessed by four publications each. Several fluoropyrimidine-based regimens were examined across the studies. These included FOLFOX regimens (5-FU, oxaliplatin and leucovorin) [14, 22, 24]and FOLFIRI (5-FU, irinotecan and leucovorin)[14] for colorectal cancer, TPF (docetaxel, cisplatin and 5-FU) for head and neck cancer [22], FOLFIRINOX (5-FU, oxaliplatin, irinotecan and leucovorin) for pancreatic cancer[17]. The two remaining publications assessed TDM interventions for tamoxifen [21] and pegasparaginase [26]. Ogungbenro et al. (2018) [25] assessed hypothetical pharmacokinetic dosing regimens for pembrolizumab and nivolumab [25].

Table 4 presents an overview of the dosing outcomes and target ranges of the TDM interventions. In studies presenting dosing outcomes, 5-FU concentrations were considered subtherapeutic in two studies for patients with colorectal cancer [22, 24]. Over half of patients had low concentrations of tamoxifen[21] and imatinib[23] for breast cancer and gastrointestinal stromal tumour (GIST), respectively. Pegasparaginase [26], pembrolizumab and nivolumab[27] were considered to be used at supratherapeutic therapeutic doses.

Study quality

The study quality was assessed for each of the eight economic evaluations from the six full-text articles identified using the CHEERS Checklist by one reviewer (DV) (Table 2). Overall study quality was good with a median 80% of applicable items being met (minimum 61%, maximum 91%). None of the included studies met the requirement to describe and give reasons for the type of economic model used (CHEERS Checklist item 15: 'Describe and give reasons for the specific type of decision-analytical model used'). Only two of five economic evaluations that presented cost-utility analyses described the population and methods used to elicit outcome preferences (utilities) [22]. Half of the full-text economic evaluations adequately described the clinical effectiveness data or describe the methods of

identifying clinical effectiveness data[22, 27]. Three of six publications did not state the sources of funding [24, 26, 27].

Model type

Markov models were the most common type of model and were used in 4 publications [15, 16, 21, 24]. Partitioned survival model[23]and a decision-tree[14] were used in one publication each. None of the publications provided a justification for the type of model chosen. A summary of the economic models is presented in Table 2.

Perspective

The majority of economic evaluations were conducted from the perspective of the health care sector or health care payer. Economic evaluations from the health care sector perspective take into account formal health care costs but does not include other considerations such as patients time costs. Economic evaluations from a payer perspective may not include not borne by the payer such as out-of-pocket costs [30]. Two publications [22, 26] stated that they performed their analysis from a health care sector perspective, one of which was limited to hospital system [26]. One publication stated that it used a "health system as payer" perspective [14] while three publications had a payer perspective, either as a third-party payer perspective or health care payer more broadly [13, 17, 21, 24, 27]. One publication stated that it used a societal perspective and a health care perspective [23]. However, this study included similar health-related costs and outcomes to the other studies [23]. This may be because the societal perspective can focus on health care costs and benefits from a "public interest" perspective [30]. Most studies did not state how the study perspective resulted in the inclusion or exclusion of particular costs or benefits. Two studies, both abstract publications, did not report the economic evaluation perspective [15, 16].

Time horizon

The time horizons used in the economic evaluations varied substantially across the publications, ranging from less than one year to lifetime. One TDM publication presented a cost-analysis that had a time horizon of less than one year that corresponded to a single course of treatment [26]. Two publications [13, 23]had a model duration of 5 years. Six publications presented lifetime models[[14-17, 21, 24]and one publication presented two 20-year models[22]. The hypothetical pharmacokinetic dosing publication also presented two cost-analyses that corresponded to a single course of treatment[27].

Discount rate

Discount rates varied from [14] 1.5% to 4.5% per annum with four studies using a discount rate of 3% per annum [13, 15, 24], one study using a discount rate of 3.5% per annum [22] for costs and outcomes. Two studies used different rates to discount costs and outcomes. Discount rates of 4.5% and 1.5%, and 4% and 1.5%, per annum for costs and outcomes, respectively, were used by the studies as recommended by Dutch guidelines [21, 23].

Sources of clinical effectiveness data

A range of data sources were used to inform the clinical effectiveness of TDM interventions. A summary of the key clinical data use in the economic evaluations is presented in Table 4. Only one publication[13] appeared to have used data directly from a randomised trial that compared imatinib with TDM to standard imatinib treatment in CML. The trial reported a difference in major molecular response [5], which is a surrogate outcome for overall survival [31, 32]. One study used propensity score adjusted observational data to inform TDM effectiveness [17] and another used retrospective clinical records [26].

Several studies used multiple data sources to model the clinical effectiveness of TDM. Two studies [21, 23]used published retrospective analyses (RCT and cohort study) to estimate outcomes by plasma concentration which were applied to proportions of patients estimated to

be in each plasma concentration category. Three publications [21, 22, 24]. that presented four TDM economic evaluations used clinical data from several sources to model the clinical effectiveness of TDM. Two economic evaluations that assessed 5-FU TDM in colorectal cancer used both randomised and non-randomised TDM studies and a randomised study of different chemotherapy regimens to inform clinical effectiveness [22, 24]. .

Of the three studies that assessed 5-FU in colorectal cancers[14, 22, 24], only one[14] considered 5-FU TDM in a regimen containing bevacizumab, an established standard of care [33, 34].

The use of clinical data from several sources may introduce bias due to differences in the chemotherapy regimens used in the studies, differences in baseline patient characteristics, and improvements in treatment practices over time [3, 22, 24, 35, 36]. Notably, the results of the head and neck cancer model were considered "speculative" by the authors due to the limited clinical evidence supporting 5-FU TDM [22].

One study [27] was informed by pharmacokinetic and pharmacodynamics simulation models which demonstrated similar area under the curve (AUCs) with the implicit assumption that achieving similar AUCs would produce similar efficacy outcomes.

Reporting of costs

The net difference in costs ranged from -$269,783 to $56,234 across the eleven studies that reported costs differences (Table 6). Five publications [21-24, 26] reported the cost of the TDM intervention to range from $84 to $267. Two publications reported the cost of TDM to include blood collection, testing, and clinician costs for dose revision [22, 26]. Three publications did not explicitly state whether the stated assay cost included the cost of collection and clinician costs [21, 23, 24]. The study of hypothetical pharmacokinetic dosing regimens for pembrolizumab and nivolumab [27] that reported large cost savings (greater

than $40,000) performed cost-analyses that examined cost savings per treatment course of over $900,000 per treatment course compared with the standard dosing regimen. The study developed weight-based ‘dose bands’ that would achieve an AUC similar to a ‘typical’ 75 kg patient using standard dosing. Therefore, this study did not include TDM assay costs [27].

Cost-effectiveness of TDM

The results of the economic models are presented in Table 6. Eight publications reported ICERs as the cost per QALY gained [14-16, 21-24]. ICERs ranged from -$175,886/QALY (dominant) to $76,027/QALY. One publication [17] reported an ICER of $13,168 per life LYG. All publications considered TDM to be cost-effective based on an ICER below their willingness-to-pay threshold (7 publication) or being cost-saving (4 publications). Three of the abstracts did not state a willingness-to-pay threshold[13-15].

Discussion

The economic evaluations of TDM for cancer treatments identified in this review consistently considered the TDM to be a cost-effective intervention. The cost-utility analysis with the highest ICER (Zuidema et al. (2019) [23]) may be due to the shorter five-year time horizon used. This approach appeared conservative compared with longer time horizons used in the two metastatic colorectal cancer evaluations [22, 24].

The main shortcomings in publication quality as assessed by the CHEERS framework were lack of reasoning for the type of decision analytic model, justification of the time horizon, description on the methods used the derive utility values, and no justification on the use of a single study. This may be in part due to limitations in publication length. The two economic models presented in Freeman et al. (2015) [22] were presented in a comprehensive report format that met most of the CHEERS criteria. None of the publications reported reasons for the type of decision-analytical model used in the economic evaluation. We hypothesise that

the frequent use of Markov and partitioned survival models for economic evaluations of cancer treatments have resulted in these modelling approaches becoming default choices, resulting publications not providing a rationale for their use [8, 9].

Another key limitation of several economic models was that they relied on lower quality clinical evidence such as retrospective cohort studies or patient records[17, 21, 26] or other less robust sources of evidence[22, 24]. This was true of the Ogungbenro et al. (2018) [27] study of hypothetical pharmacokinetic dosing regimens. A prospective study of tamoxifen efficacy by serum endoxifen level did not find an association between endoxifen levels and objective response rate in postmenopausal women using tamoxifen for estrogen receptor–positive breast cancer in the neoadjuvant or metastatic setting [37]. However, it is unclear whether these findings would apply to the adjuvant breast cancer setting in the van Nuland et al. (2018) [21] model considered in this paper. As the economic benefit of a TDM intervention relies on its estimated clinical effectiveness, uncertainty in the underlying clinical studies also contributes to uncertainty in the results of an economic evaluation. Therefore, the strength of the clinical evidence and the plausibility of clinical outcomes extrapolated beyond the study duration [38] should be discussed in future economic evaluations of TDM interventions.

Future economic evaluations of TDM for fluoropyrimidine-based chemotherapy regimens for the treatment colorectal cancer should consider the use of targeted treatments that are a part of current standard of care [34]. Of the studies that assessed 5-FU as a first-line treatment for advanced colorectal cancer[14, 22, 24], only one[14] considered 5-FU TDM in a regimen containing bevacizumab, despite bevacizumab being recommended by European guidelines since 2009 and US guidelines since 2011 [39]. Becker et al.(2013) [14] considered the cost-effectiveness of TDM for regimens containing bevacizumab and reported similar ICERs for corresponding regimens both with or without bevacizumab. Nonetheless, longer use of

newer, high cost treatments as a result of TDM reducing treatment toxicity or improving efficacy has the potential to change the ICER of a TDM intervention.

TDM interventions are likely to be cost-effective in an oncology landscape where treatments offering small benefits have high cost. Many short term non-randomised studies used to inform the economic evaluations show reductions in AEs that are likely to be patient-relevant and reduction hospital resource use. However, economic evaluations relying on less robust evidence may be less persuasive to decision-makers as health technology assessment bodies have a strong preference for direct evidence from RCTs [40]. Due to the difficulties conducting RCTs for TDM interventions in oncology [41], good quality observational studies may provide robust estimates on the effectiveness of TDM [42]. There may be scope for observational studies using real-world data to evaluate concentration-effect and concentration-toxicity relationships, particularly for patient groups typically excluded from clinical trials such as older patients and patients with comorbid conditions affecting drug metabolism [43].

One of the key limitations in the comprehensive review is the inherent subjectivity of assessing the quality of economic evaluations [44, 45]. The CHEERS Checklist, although used frequently to assess the quality of published economic evaluations, is a guidance for the reporting economic evaluations, rather than the methodological quality of the economic evaluation[20]. Therefore, this review is limited to assessing what has been reported [20]. Due to the potential subjectivity of checklists, the review may have benefited from an additional reviewer performing the quality assessment and the use of a methodological checklist such as the Quality of Health Economic Studies (QHES) checklist [46].

Despite the reported cost-effectiveness of TDM for several cancer treatments, barriers remain to its implementation. In addition to the aforementioned difficulties establishing therapeutic

ranges, logistical challenges and difficulties with cyclic administration other implementation challenges remain. It has been noted that clinicians may be reluctant to implement dose adjustments based on TDM. For this reason, a prospective study by Groenland et al. (2019) are examining only dose increases in the case of low exposure and physician adherence as a secondary outcome in their study of TDM in oral anticancer drugs [41]. Although one study stated that it considered a societal perspective [23], none of the economic evaluation explicitly considered additional patient or caregiver-time costs or transport that may be incurred if additional consultations are required for monitoring or dose adjustment.

Future economic evaluations of TDM for cancer drugs may need to more explicitly address and explore uncertainties around underlying clinical effectiveness using scenario analyses. Future clinical studies and economic evaluation of 5-FU TDM in metastatic colorectal cancer and other cancers where several targeted therapies are used, may benefit from the inclusion of targeted therapies that are standard of care.

Conclusion

This comprehensive review found that TDM interventions for cancer treatments were considered cost-effective across studies. The quality of the economic evaluations was good however, some of the clinical evidence supporting the economic evaluations was of poor quality. Future research assessing the impact of TDM on overall survival or long-term health outcomes may enhance the evidence base for TDM in oncology. Future economic evaluations of TDM for cancer treatments will benefit from exploring uncertainties in the underlying clinical evidence the incorporation of newer treatments used alongside or after the TDM treatment that form the current standard of care and additional clinical evidence.

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Table 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4,
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 (quality assessment)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 (quality assessment)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p6-7 Table 2-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p8, Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p11-12; Tables 3 and 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p11-12
Risk of bias across	22	Present results of any assessment of risk of bias across studies (see Item 15).	p8, Table 4

studies			
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p13-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p17

Table 2: Overview of the economic evaluations

Publication	Model type	Perspective	Time horizon	Discount rate (per annum)	Quality Assessment [a]
Full text articles					
van Nuland et al. [21]	Markov	Healthcare payer	Lifetime	4.5% (costs) 1.5% (outcomes)	78%
Freeman et al. [22]	Markov	Healthcare sector	20 years	3.5%	91%
Freeman et al. [22]	Markov	Healthcare sector	20 years	3.5%	91%
Zuidema et al. [23]	Partitioned survival	Societal	5 years	4% (costs) 1.5% (outcomes)	78%
Goldstein et al. [24].	Markov	Third party payer	Lifetime	3%	61%
Kloos et al. [26]	Cost analysis	Healthcare payer	Short-term	No discounting	86%
Abstracts					
Kim et al. [15]	Markov	Not reported	Lifetime	3%	NA
Salamone et al. [13]	Not reported	Healthcare payer	5 years	3%	NA
Kim et al. [16]	Markov	Not reported	Lifetime	Not stated	NA
Becker et al. [14]	Decision tree	Health system	Lifetime	3%	NA
Egues et al. [17]	Not stated	Healthcare payer	Lifetime	3%	NA
Non-TDM study (hypothetical pharmacokinetic dosing study)					
Ogungbenro et al. [27] (pembrolizumab)	Cost analysis	Healthcare payer	Short-term	No discounting	77%
Ogungbenro et al. [27] (nivolumab)	Cost analysis	Healthcare payer	Short-term	No discounting	81%

NA, not applicable;

[a] Proportion of applicable items met on the CHEERS Checklist

Table 3: Summary of TDM interventions assessed in the economic evaluations

Publication (country)	Cancer	Intervention	Comparator
Full text articles			
van Nuland et al. [21] (Netherlands)	Breast (ER+, local)	Tamoxifen + 3 monthly endoxifen (active metabolite) TDM and dose adjustment	Tamoxifen 20 mg daily
Freeman et al. [22] (UK)	Colorectal (metastatic)	5-FU (with folinic acid or FOLFOX6 regimen) and dose adjustment monitoring	5-FU (FV-LV or FOLFOX6)
	Head and neck	5-FU (with docetaxel and cisplatin) and TDM and dose adjustment	5-FU (with taxane and cisplatin)
Zuidema et al. [23] (Netherlands)	GIST (metastatic)	Imatinib (first measurement at 14 days)	Imatinib 400 mg daily
Goldstein et al. [24]. (USA)	Colorectal (metastatic)	5-FU (with FOLFOX regimen) with TDM	5-FU (FOLFOX)
Kloos et al. [26] (Netherlands)	ALL	Pegasparaginase monitoring	E.coli asparaginase (3 doses) + Pegasparaginase (2,500 IU/m2)
			Pegasparaginase (1,500 IU/m2, hypothetical)
Abstracts			
Kim et al. [15] (USA)	CML	Imatinib with TDM and dose escalation (no TDM intervention details)	Imatinib 400 mg daily
Salamone et al. [13] (USA)	CML	Imatinib with TDM and dose escalation	Imatinib 400 mg daily
Kim et al. [16] (USA)	CML	Imatinib with TDM and dose escalation	Imatinib 400 mg daily
Becker et al. [14] (UK)	Colorectal (metastatic)	5-FU (FOLFOX, FOLFIRI ± bevacizumab or 5-FU-LV) and TDM	FOLFOX, FOLFIRI (± bevacizumab) or 5-FU-LV
Egues et al. [17] (Spain)	Pancreatic (metastatic)	5-FU (FOLFIRINOX) TDM	FOLFIRINOX
Non-TDM study (hypothetical pharmacokinetic dosing study)			
Ogungbenro et al. [27] (UK)	Melanoma (advanced)	Pembrolizumab pharmacokinetic dose banding [a]	Pembrolizumab 2 mg kg-1 every 3 weeks

Publication (country)	Cancer	Intervention	Comparator
	Melanoma (advanced)	Nivolumab pharmacokinetic dose banding [a]	Nivolumab 3mg kg-1 every 2 weeks.

ALL, acute lymphoblastic leukaemia; AUC = area under the curve; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CML, chronic myeloid leukaemia; ER+, oestrogen receptor alpha positive; FA, folinic acid; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFOX6, FOLFOX regimen administered every two weeks; GIST, gastro intestinal stromal tumours; NA, not applicable; TDM, therapeutical drug monitoring; UK, United Kingdom; USA, United States of America; 5-FU = 5-fluorouracil; 5-FU-LV, 5-fluorouracil and folinic acid

[a] Doses determined using simulation that would maintain AUC of typical 75 kg patient accounting for vial size.

Table 4: TDM dosing outcomes and target ranges examined in the economic evaluations

Publication	TDM Intervention	Dosing outcomes	Target
Full text articles			
van Nuland et al. [21]	Tamoxifen (endoxifen)	24% under-dosed (baseline) 6% overdosed (dose reduction)	≥ 5.97 ng/Ml (steady state)
Freeman et al. [22]	5-FU (with folinic acid or FOLFOX6)	64% under-dosed (dose increased) 19% overdosed (dose reduction)	2.5 to 3 mg/L AUC 20-24 mg·h·L−1
	5-FU (with docetaxel and cisplatin)	30% mean dose reduction	AUC $_{0\text{-}48}$ 7,200 – 13,000 ng.h/mL
Zuidema et al. [23]	Imatinib	55.7% under-dosed 2.9% overdosed	1000–3200 mcg/L (trough)
Goldstein et al. [24].	5-FU (with FOLFOX regimen)	64% under-dosed (dose increased) 19% overdosed (dose reduction)	2.5 to 3 mg/L $AUC_{0\text{-}8}$ 20-24 mg·h·L−1
Kloos et al. [26]	Pegasparaginase	44% fewer IU of pegasparaginase	trough asparaginase activity level 100–250 IU/l.
Abstracts			
Kim et al. [15]	Imatinib with TDM and dose escalation (no TDM intervention details)	Not reported	Not reported
Salamone et al. [13]	Imatinib with TDM and dose escalation (Cmin > 1000 ng ml-1)	Not reported	Cmin ≥ 1000 ng/ml
Kim et al. [16]	Imatinib with TDM and dose escalation (no TDM intervention details)	Not reported	Not reported
Becker et al. [14]	5-FU (FOLFOX, FOLFIRI ± bevacizumab or 5-FU-LV) and TDM	Not reported	Not reported
Egues et al. [17]	5-FU (FOLFIRINOX)	Not reported	Not reported
Non-TDM study (hypothetical pharmacokinetic dosing study)			
Ogungbenro et al. [27]	Pembrolizumab pharmacokinetic dose banding [b]	83% overdosed 0% underdosed	Doses determined using simulation that would maintain AUC of typical 75 kg patient accounting for vial size.
	Nivolumab pharmacokinetic dose banding [b]	58% overdosed 29% underdosed	

AUC = area under the curve; FA, folinic acid; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFOX6, FOLFOX regimen administered every two weeks; NA, not applicable; TDM, therapeutical drug monitoring; 5-FU = 5-fluorouracil; 5-FU-LV, 5-fluorouracil and folinic acid

Table 5: Overview of clinical effective data used in the economic evaluations

Publication (country)	Patient population (model)	Main clinical data (TDM)	Main clinical data (comparator)
Full text articles			
van Nuland et al. [21]	Breast	Secondary analysis of cohort study (N=1,370) Endoxifen levels < 5.97 ng/ml had greater recurrence (HR = 0.74; 95% CI, 0.55–1.00) [47]	
Freeman et al. [22]	Colorectal	Non-randomised study (allocation to TDM based on usual care at study site) N=118 [36] TDM PFS 16 months (vs 10 months) TDM OS 28 months (vs 22 months)	
	Head and neck	HR PFS=0.966 based on limited clinical data. No OS benefit in base case.	
Zuidema et al. [23]	GIST	Randomised PK study (N=79) [48] C_{trough} >1,100 ng/mL had better TTP (HR = 0.418; 95% CI, 0.231–0.756)	
Goldstein et al. [24].	Colorectal	Non-randomised study (allocation to TDM based on usual care at study site) N=118 [36] TDM PFS 16 months (vs 10 months) TDM OS 28 months (vs 22 months)	Randomised trial (N=226) [35] PFS 8.7 months OS 19.2 months
Kloos et al. [26]	ALL	Retrospective study of patient records (N=134) Assumed equivalent effectiveness	
Abstracts			
Kim et al. [15]	CML	Not reported	
Salamone et al. [13]	CML	Randomised trial (N=139) [5] $C_{trough <}$ 1000 ng/mL randomised to TDM or standard dosing 63% major molecular response at 1 year in TDM arm (vs 37% in standard dosing)	
Kim et al. [16]	CML	Not reported	
Becker et al. [14]	Colorectal	Not reported	
Egues et al. [17]	Pancreatic	Retrospective patient records (N=52)	
Non-TDM study (hypothetical pharmacokinetic dosing study)			

Publication (country)	Patient population (model)	Main clinical data (TDM)	Main clinical data (comparator)
Ogungbenro et al. [27]	Melanoma	PK PD simulation studies to maintain AUC of 'typical' 75 kg patient. Assumed equivalent effectiveness based on same AUC.	

ALL, acute lymphoblastic leukaemia; AUC, area under the curve; CML, chronic myeloid leukaemia; C_{trough} , trough concentration; ER+, oestrogen receptor alpha positive; GIST, gastro intestinal stromal tumours; HR, hazard ratio; N= number of patients in study; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; TDM, therapeutical drug monitoring; TTP = time to progression

Table 6: Results of the economic evaluations (costs in 2018 USD)

Publication	Cancer	TDM intervention	Time horizon	Net difference (cost)	Net difference (effect)	ICER/ICUR	WTP threshold
Full text articles							
van Nuland et al. [21]	Breast	Tamoxifen	Lifetime	-$2,023	0.0115 QALYs	Dominant (-$175,886/QALY)	$25 866 to $103,463
Freeman et al. [22]	Colorectal	5-FU	20 years	$3,914	0.599 QALYs	$6,539/QALY	$31,526
Freeman et al. [22]	Head and neck	5-FU	20 years	$449	0.014 QALYs	$32,450/QALY [a]	
Zuidema et al. [23]	GIST	Imatinib	5 years	$56,234	0.74 QALYs	$76,027/QALY	$103,463
Goldstein et al. [24].	Colorectal	5-FU	Lifetime	$14,107	0.57 QALYs	$21,424/QALY	$52,669 to $105,337
Kloos et al. [26]	ALL	Pegasparaginase	Short-term	-$13,601	NA	NA	NA
Abstracts							
Kim et al. [15]	CML	Imatinib	Lifetime	$2,358	0.149 QALYs	$15,834/QALY	Not reported
Salamone et al. [13]	CML	Imatinib	5 years	-$27,296	0.25 QALYs	Dominant (-$109,184/QALY)	Not reported
Kim et al. [16]	CML	Imatinib	Lifetime	$3,344	0.085 QALYs	$39,126/QALY	$100,000
Becker et al. [14]	Colorectal	5-FU	Lifetime	Not reported	Not reported	$11,564/QALY (weighted)	Not reported
Egues et al. [17]	Pancreatic	5-FU	Lifetime	$3,291	0.25 LYG	$13,168/LYG	$47,396
Non-TDM study (hypothetical pharmacokinetic dosing study)							
Ogungbenro et al. [27]	Melanoma	Pembrolizumab	Short-term	-$263,783	NA	NA	NA
	Melanoma	Nivolumab	Short-term	-$48,684	NA	NA	NA

ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYG, life year gained; NA, not applicable; QALY, quality-adjusted life year; US = United States Dollars; WTP, willingness to pay

[a] The ICER was considered speculative by the authors due to limited clinical information to inform the cost-effectiveness modelling

Figure 1: PRISMA flow chart

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TDM, therapeutic drug monitoring

Appendix 1: Medline Ovid Search Strategy

1	cancer.mp. or exp Neoplasms/
2	carcinoma.mp
3	neoplasm.mp.
4	leuk?emia.mp.
5	lymphoma.mp.
6	((cyclophosphamide or chlorambucil or melphalan or chlormethine or ifosfamide or trofosfamide or prednimustine or bendamustine or busulfan or treosulfan or mannosulfan or thiotepa or triaziquone or carboquone or carmustine or lomustine or semustine or streptozocin or fotemustine or nimustine or ranimustine or uramustine or etoglucid or mitobronitol or pipobroman or temozolomide or dacarbazine or methotrexate or raltitrexed or pemetrexed or pralatrexate or mercaptopurine or tioguanine or cladribine or fludarabine or clofarabine or nelarabine or cytarabine or fluorouracil or tegafur or carmofur or gemcitabine or capecitabine or azacitidine or decitabine or floxuridine or fluorouracil or tegafur or trifluridine or vinblastine or vincristine or vindesine or vinorelbine or vinflunine or vintafolide or etoposide or teniposide or demecolcine or paclitaxel or docetaxel or paclitaxel or cabazitaxel or trabectedin or dactinomycin or doxorubicin or daunorubicin or epirubicin or aclarubicin or zorubicin or idarubicin or mitoxantrone or pirarubicin or valrubicin or amrubicin or pixantrone or bleomycin or plicamycin or mitomycin or ixabepilone or cisplatin or carboplatin or oxaliplatin or satraplatin or polyplatillen or procarbazine or edrecolomab or rituximab or trastuzumab or gemtuzumab or cetuximab or bevacizumab or panitumumab or catumaxomab or ofatumumab or ipilimumab or brentuximab or pertuzumab or obinutuzumab or dinutuximab or nivolumab or pembrolizumab or blinatumomab or ramucirumab or necitumumab or elotuzumab or daratumumab or mogamulizumab or inotuzumab or olaratumab or durvalumab or bermekimab or avelumab or atezolizumab or porfimer or aminolevulinic or temoporfin or efaproxiral or padeliporfin or imatinib or gefitinib or erlotinib or sunitinib or sorafenib or dasatinib or lapatinib or nilotinib or temsirolimus or everolimus or pazopanib or vandetanib or afatinib or bosutinib or vemurafenib or crizotinib or axitinib or ruxolitinib or ridaforolimus or regorafenib or masitinib or dabrafenib or ponatinib or trametinib or cabozantinib or ibrutinib or ceritinib or lenvatinib or nintedanib or cediranib or palbociclib or tivozanib or osimertinib or alectinib or rociletinib or cobimetinib or midostaurin or olmutinib or binimetinib or ribociclib or brigatinib or lorlatinib or neratinib or encorafenib or dacomitinib or icotinib or abemaciclib or amsacrine or asparaginase or altretamine or hydroxycarbamide or lonidamine or pentostatin or miltefosine or masoprocol or estramustine or tretinoin or mitoguazone or topotecan or tiazofurine or irinotecan or alitretinoin or mitotane or pegaspargase or bexarotene or arsenic or denileukin or bortezomib or celecoxib or anagrelide or oblimersen or sitimagene or vorinostat or romidepsin or omacetaxine or eribulin or panobinostat or vismodegib or aflibercept or carfilzomib or olaparib or idelalisib or sonidegib or belinostat or ixazomib or talimogene or venetoclax or vosaroxin or niraparib or rucaparib or etirinotecan or plitidepsin or epacadostat or enasidenib or talazoparib or copanlisib) adj2 (level* or monitor*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	drug monitoring.mp. or exp Drug Monitoring/
8	therapeutic drug monitoring.mp.
9	drug concentration.mp.

10	pharmacokinetic*.mp.
11	(drug* adj2 (level* or monitor*)).mp.
12	(trough adj2 level*).mp.
13	((Dose or dosage) adj2 (optimiz* or optimis* or adjust*)).mp
14	Cost-Benefit Analysis/ or cost benefit*.mp.
15	Cost effectiveness*.mp.
16	Cost utility*.mp.
17	Economics, Pharmaceutical/ or exp Economics/ or economic.mp.
18	(economic* or pharmaco?economic*).mp
19	Quality-Adjusted Life Years.mp. or exp Quality-Adjusted Life Years/
20	1 or 2 or 3 or 4 or 5
21	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
22	14 or 15 or 16 or 17 or 18 or 19
23	20 and 21 and 22
24	limit 23 to English language

Appendix 2: Embase Search Strategy

1	cancer.mp. or exp Neoplasms/
2	carcinoma
3	neoplasm
4	leuk?emia
5	lymphoma
6	(cyclophosphamide OR chlorambucil OR melphalan OR chlormethine OR ifosfamide OR trofosfamide OR prednimustine OR bendamustine OR busulfan OR treosulfan OR mannosulfan OR thiotepa OR triaziquone OR carboquone OR carmustine OR lomustine OR semustine OR streptozocin OR fotemustine OR nimustine OR ranimustine OR uramustine OR etoglucid OR mitobronitol OR pipobroman OR temozolomide OR dacarbazine OR methotrexate OR raltitrexed OR pemetrexed OR pralatrexate OR mercaptopurine OR tioguanine OR cladribine OR fludarabine OR clofarabine OR nelarabine OR cytarabine OR fluorouracil OR tegafur OR carmofur OR gemcitabine OR capecitabine OR azacitidine OR decitabine OR floxuridine OR fluorouracilor OR tegafuror OR trifluridineor OR vinblastine OR vincristine) NEXT/2 (level* OR monitor*)
7	(cyclophosphamide OR chlorambucil OR melphalan OR chlormethine OR ifosfamide OR trofosfamide OR prednimustine OR bendamustine OR busulfan OR treosulfan OR mannosulfan OR thiotepa OR triaziquone OR carboquone OR carmustine OR lomustine OR semustine OR streptozocin OR fotemustine OR nimustine OR ranimustine OR uramustine OR etoglucid OR mitobronitol OR pipobroman OR temozolomide OR dacarbazine OR methotrexate OR raltitrexed OR pemetrexed OR pralatrexate OR mercaptopurine OR tioguanine OR cladribine OR fludarabine OR clofarabine OR nelarabine OR cytarabine OR fluorouracil OR tegafur OR carmofur OR gemcitabine OR capecitabine OR azacitidine OR decitabine OR floxuridine OR fluorouracilor OR tegafuror OR trifluridineor OR vinblastine OR vincristine) NEXT/2 (level* OR monitor*)
8	(cabozantinib OR ibrutinib OR ceritinib OR lenvatinib OR nintedanib OR cediranib OR palbociclib OR tivozanib OR osimertinib OR alectinib OR rociletinib OR cobimetinib OR midostaurin OR olmutinib OR binimetinib OR ribociclib OR brigatinib OR lorlatinib OR neratinib OR encorafenib OR dacomitinib OR icotinib OR abemaciclib OR amsacrine OR asparaginase OR altretamine OR hydroxycarbamide OR lonidamine OR pentostatin OR miltefosine OR masoprocol OR estramustine OR tretinoin OR mitoguazone OR topotecan OR tiazofurine OR irinotecan OR alitretinoin OR mitotane OR pegaspargase OR bexarotene OR arsenic OR denileukin OR bortezomib OR celecoxib OR anagrelide OR oblimersen OR sitimagene OR vorinostat OR romidepsin OR omacetaxine) NEXT/2 (level* OR monitor*)
	(eribulin OR panobinostat OR vismodegib OR aflibercept OR carfilzomib OR olaparib OR idelalisib OR sonidegib OR belinostat OR ixazomib OR talimogene OR venetoclax OR vosaroxin OR niraparib OR rucaparib OR etirinotecan OR plitidepsin OR epacadostat OR enasidenib OR talazoparib) NEXT/2 (level* OR monitor*)
	(vindesine OR vinorelbine OR vinflunine OR vintafolide OR etoposideor OR teniposideor OR demecolcine OR paclitaxel OR docetaxel OR paclitaxeloror OR cabazitaxel OR trabectedin OR dactinomycin OR doxorubicin OR daunorubicin OR epirubicin OR aclarubicin OR zorubicin OR idarubicin OR mitoxantrone OR pirarubicin OR valrubicin OR amrubicin OR pixantrone OR bleomycin OR plicamycin OR mitomycin OR ixabepilone OR cisplatin OR carboplatin OR oxaliplatin OR satraplatin OR polyplatillen OR procarbazine OR edrecolomab OR rituximab OR trastuzumab OR gemtuzumab OR cetuximab OR bevacizumab OR panitumumab) NEXT/2 (level* OR monitor*)

Appendix 3: Centre for Reviews and Dissemination (CRD) databases: Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHSEED), and Health Technology Assessment (HTA) database

(therapeutic drug monitoring) OR (drug monitoring)