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Analysis of factors associated with use of real-world data in single technology appraisals of cancer drugs by the National Institute for Health and Care Excellence

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ABSTRACT

Objectives: This study investigates factors associated with use of real-world data (RWD) in economic modelling for single technology appraisals (STAs) of cancer drugs by the National Institute for Health and Care Excellence (NICE) to improve systematic understanding of the use of RWD.

Methods: The data were extracted from STAs of cancer drugs, for which NICE issued guidance between January 2011 and December 2022 (n=267). Binary regression was used to test hypotheses concerning the greater or lesser use of RWD. Bonferroni-Holm correction was used to control error rates in multiple hypotheses tests. Several explanatory variables were considered in this analysis, including time (*Time*), incidence rate of disease (*IR*), availability of direct treatment comparison (*AD*), generalisability of trial data (*GE*), maturity of survival data in trial (*MS*) and previous technology recommendations by NICE (*PR*). The primary outcome variable was *any* use of RWD. Secondary outcome variables were specific uses of RWD in economic models.

Results: AD had a statistical negative association with *any* use of RWD whereas no associations with *non-parametric* and *parametric* use of RWD were found. *Time* had several statistical associations with use of RWD (validating survival distributions for the intervention, estimating progression-free survival for the intervention, estimating overall survival for comparators and transition probabilities).

Conclusions: RWD were more likely to be used in economic modelling of cancer drugs when randomised controlled trials failed to provide relevant clinical information of the drug for appraisals, particularly in the absence of direct treatment comparisons. These results, based on analysis of data systematically collected from previous appraisals, suggest that uses of RWD were associated with data gaps in the economic modelling. While this result may support some of the claimed advantages of using RWD when evidence is absent, the question, the extent to which use of RWD in indirect treatment comparisons reduces uncertainty is still to be determined.

1. Introduction

The integration of real-world data (RWD) into health technology assessment (HTA) decision-making has drawn significant attention. The National Institute for Health and Care Excellence (NICE) has shown keen interest in the use of RWD. Incorporating RWD into HTA decision-making is expected to reduce gaps in knowledge and increase patient access to innovative medicines [1]. In June 2022, NICE introduced a real-world evidence (RWE) framework, aiming to leverage RWD in their production of guidance [2]. This framework identifies areas where RWD can be used in decision-making, including where randomised controlled trials (RCTs) are of poor quality, where there is a lack of long-term follow-up and questions concerning generalisability of the results.

RWD can play a crucial role in drug appraisals when clinical trial evidence is insufficient to support HTA decisions. Employing RWD in economic modelling can help reduce uncertainty by supplying additional information. For example, RWD can validate the generalisability of outcomes observed in clinical trials. Given that clinical trial

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participants are typically younger and fitter than those in routine clinical practice [3], RWD can aid decision-makers in assessing how well clinical trial data represent routine practice. Another area often mentioned for use of RWD is to appraise health technologies for rare diseases involving small patient populations [4]. Clinical trials for health technologies for rare diseases or specific subpopulations often have limited sample sizes, making it challenging to assess the impact of the technologies. RWD, with its larger and more diverse datasets, can contribute to better understanding of clinical practice and patient experience.

Furthermore, RWD can offer valuable information in cases with limited robust evidence, such as single-arm trials or the absence of long-term information [5]. When clinical trial evidence for comparators is not sufficient, RWD may be used for indirect treatment comparison. For example, in NICE technology appraisal (TA) guidance of mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy (NICE TA855) [6], RWD were used to synthesise an external control arm as the main clinical evidence for mobocertinib was a single-arm trial. This informs decision-makers about the comparative treatment effect despite the absence of trial data. Also, RWD can provide long-term data from routine clinical practice when clinical trial data are too immature to provide adequate long-term information, such as the subsequent treatments used in routine clinical practice. HTA requires understanding of the long-term impact of an intervention on patient outcomes. RWD can provide long-term clinical outcomes collected over extended periods, which are often difficult to assess from short-term clinical trials.

The few studies that have reviewed the use of RWD in HTA decision making [7–12] show that awareness of the value, and use of RWD, in HTA decision making has increased over time. The value of RWD described in these studies is often to provide information in situations where RCTs provided limited information. While these studies illustrate the scope for use of RWD, no study has reviewed whether these situations are associated with use of RWD in economic modelling. Beyond documenting the scope for use of RWD, systematic research, analysing use of RWD in economic modelling for drug appraisals, is needed to understand in which situation RWD are more likely to be used. Investigating what factors are associated with use of RWD is essential to improve systematic understanding of its previous use in economic modelling. It might contribute to understanding the pattern of actual use and facilitators or barriers to more extensive use of RWD. Furthermore, it could indicate where RWD might be more useful in economic modelling. Understanding which situation is associated with greater or less use of RWD can help HTA bodies respond to future cases and provide better guidance by prioritising areas where RWD are more likely to be useful to improve economic modelling.Therefore, this study aims to investigate factors associated with greater use of RWD in economic models of cancer drug appraisals by NICE.

2. Methods

This study uses data from 267 NICE single technology appraisals (STAs) of oncology medicines, for which NICE issued guidance between January 2011 and December 2022. The data were extracted following a protocol specially developed to document information about the use of RWD in economic modelling in NICE STAs of oncologic medicines [13]. Extracted data include clinical evidence-related information, such as availability of primary clinical evidence, used for explanatory variables, and the use of RWD in economic models, for outcome variables. Regression models were used to analyse associations between use of RWD and a range of factors. A binary multivariate logistic regression was used as the outcome variables, different types of *use of RWD,* were binary.

The hypotheses tested in the binary logistic regression are summarised in Fig. 1. The primary hypothesis is that RWD are more likely to be used in economic modelling in more recent appraisals. The primary explanatory variable *Time* was measured by the month when the final appraisal determination (FAD) was issued. Six additional variables were identified for the regression analysis either because they were all potentially related to data gaps or data availability: availability of direct treatment comparison (*AD*), generalisability (*GE*), risk of bias (*RB*), incidence rate (*IR*), maturity of survival data (*MS*) and previous technology recommendation by NICE (*PR*). Literature and some NICE TA guidance were reviewed to identify cases where RCTs provide limited information, such as RCTs with lack of internal and external validity [14, 15] and clinical trials having limited or no information about comparators [16]. In such cases, RWD can be used to bridge the evidence gap in economic modelling. During interviews with HTA experts [17], maturity of survival data was suggested as a potential factor associated with greater use of RWD. In economic models for HTA decision-making, survival data are extrapolated beyond the clinical trial observation to assess long-term survival outcomes. Uncertainty around long-term effects can be introduced when this extrapolation is made based on substantially incomplete or immature survival data [18]. One of the recommended approaches is to use external data, including RWD to assess the clinical plausibility of predictions. This study hypothesises that RWD are more likely to be used in economic modelling when survival data are immature. Previous recommendation by NICE was included as an explanatory variable in order to explore the influence of data availability, since a previously recommended technology is more likely to have been used in routine clinical practice. Technology recommended by NICE was recorded in two ways: recommended for any indication, and for the same type of cancer. In this regression analysis, some categorical explanatory variables, *AD*, *MS*, *GE*, were converted to binary variables in the regression analyses. The Table 1 describes the levels distinguished for each explanatory variable.

The primary outcome variable of this study, *any use of RWD*, provides a summary of use of RWD in economic modelling. While it helps identify main factors associated with use of RWD, the use of RWD might differ

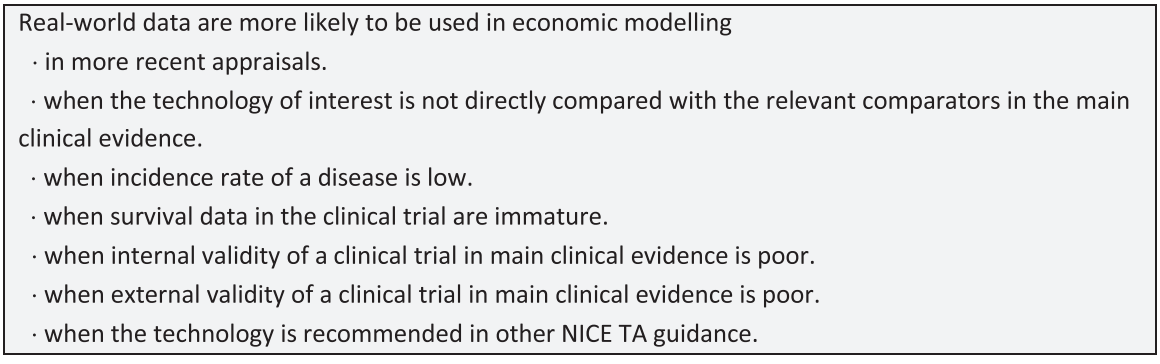

Fig. 1. Hypotheses about greater use of real-world data.

Table 1
Summary of the explanatory variables.

Variables	Description
Time	· Month-Year(MM/YYYY)
Availability of direct treatment comparison	· Whether the direct treatment comparison with agreed comparators is available in clinical trial or not: - Not available - Available for some comprators - Available for all comparators.
• *AD1*	· Available for some or all comparators · Not available
• *AD2*	· Available for all comparators · Not available or available for some
Incidence rate (*IR*)	· Number of expected patients per 10,000 (annual)
Maturity of survival data (*MS*)	· Maturity of survival data based on the proportion of deaths in a clinical trial of the intervention: - Extremely immature: Proportion of death events < 20 % - Immature: 20 % ≤ Proportion of death events ≤ 50 % - Mature: 50 % < Proportion of death events
• *MS1*	· Immature or mature · Extremely immature
• *MS2*	· Mature · Extremely immature or immature
Generalisability (*GE*)	· The extent which a clinical trial is generalisable to the UK population: - Acceptable external validity - Moderate external validity - Questionable external validity
• *GE1*	· Moderate or questionable generalisability · Acceptable generalisability
• *GE2*	· Questionable generalisability · Acceptable or moderate generalisbility
Risk of Bias of RCTs (*RB*)	· High quality of internal validity · Good quality of internal validity with minor concerns · Moderate quality of internal validity with some concerns · Low quality of internal validity with major concerns
Technology recommended by NICE (*PR*)	· Whether technology of interest is recommended by NICE: - Recommended for another indication in any type of cancer - Recommended for another indication in same type of cancer - Not recommended for another indication
• *PR1*	· Recommended for another indication in any type of cancer · Not recommended
• *PR2*	· Recommended for another indication in same type of cancer · Not recommended

depending on the purposes of its use. Given potential differences in use, outcome variables, *non-parametric* use, *parametric* use of RWD and use of RWD for individual components in the economic models, were included as outcome variables. A description of basic data analysed in this paper is presented in a separate paper [19]. Following the data extraction protocol, 31 individual components were identified where RWD can be used in economic modelling. Among them, 25 components, which had at least one observation, were used for the analysis. From seven categories, ten separate explanatory variables were used for binary logistic regression analysis. Multicollinearity was tested using a chi-squared test between categorical variables and Kendall's rank correlation between categorical variables and continuous variables before conducting the analysis. After checking the correlation between predictors, the variable *RB* had strong correlations with other variables, hence it was excluded in this study.

Analysis was carried out using the Logistic procedure in R Version 4.2.3. In order to reduce the likelihood of false rejection of null hypotheses when testing multiple hypotheses [20], Bonferroni-Holm correction was made to correct p-values and confidence intervals (*CI*) [21]. Odds ratios (*ORs*) compared the relative odds of the greater use of RWD given the exposure to the explanatory variables (*Time*, *AD, IR, MS, GE, PR*).

3. Results

1. Test for multicollinearity of variables

   A correlational analysis was conducted to investigate the relationships among the explanatory variables. Since the variables are categorical variables (except for *Time* and *IR*), Pearson chi-squared tests were used to assess the correlation between the categorical variables (Supplement 1).

   The chi-squared value for *AD* and *RB*, $\chi^2(6) = 123.827, p = 0.000$, indicates there was a strong statistical significance between the two variables. Internal validity also has positive relationships with external validity ($\chi^2(6) = 23.059, p = 0.001$) and maturity of survival data ($\chi^2(6) = 17.942, p = 0.006$).

   The correlation between *IR* and other categorical variables was tested by Kendall's rank correlation coefficient (Supplement 2). The strong negative correlations were found between *IR* and *RB* ($\tau_b = -0.313, p = 0.000$). Positive correlations were found with *AD* ($\tau_b = 0.129, p = 0.007$) and *MS* ($\tau_b = 0.189, p = 0.0001$). In the tests of multicollinearity, *RB* had multiple associations with other variables. *RB* was omitted from the regression in order to reduce multicollinearity while other variables showing correlations with some variables were still included in the regression analyses.
2. Associations with any, non-parametric and parametric use of RWD

A multiple logistic regression analysis was conducted to investigate the association between the use of RWD in economic models and six variables (*Time, IR, AD, EV, PR* and *MS*). In the models, the binary variables converted from categorical variables were used to test the different impacts on the outcome variables. The log likelihood ratio chi-square test statistic for the full model A (*any use* of RWD) $LR\chi^2_{(10)} = 39.40, p < 0.0000$, indicated that the overall model with all explanatory variables was significant.

Fig. 2 presents the odds ratios, corrected 95 % CI and corrected P-value for the full model for three different outcome variables (any use, non-parametric use, parametric use). The variable *AD1* has a negative association with any use of RWD ($OR = 0.125$, *corrected* $p = 0.01$). There was no statistical association found with either *non-parametric* use of RWD or *parametric* use of RWD.

3. Association with use of RWD in single components

Multiple logistic regression analyses were carried out to test the hypotheses regarding use of RWD for individual components of the economic model (Supplement 3).

a. Use of RWD for validating survival distribution for intervention and comparators

   Time had statistical associations with a non-parametric use, the use of RWD in validating the survival distribution for the intervention ($OR = 1.021$; *corrected CI* : $1.003 - 1.040$, *corrected* $p = 0.012$). While there was no association between *Time* and the use of RWD in validating the survival distribution for the comparators, *PR2* had a statistical association with validating survival distribution for comparators ($OR = 2.672$; *corrected CI* : $1.035 - 6.903$, *corrected* $p = 0.034$).

b. Overall survival (OS) for comparator

   Several statistical associations were found with the use of RWD for estimating OS for comparators. It had a positive association with *Time* ($OR = 1.015$, *corrected CI* : $1.000 - 1.029$; *corrected* $p = 0.043$). The negative association between *AD1* and estimating OS for

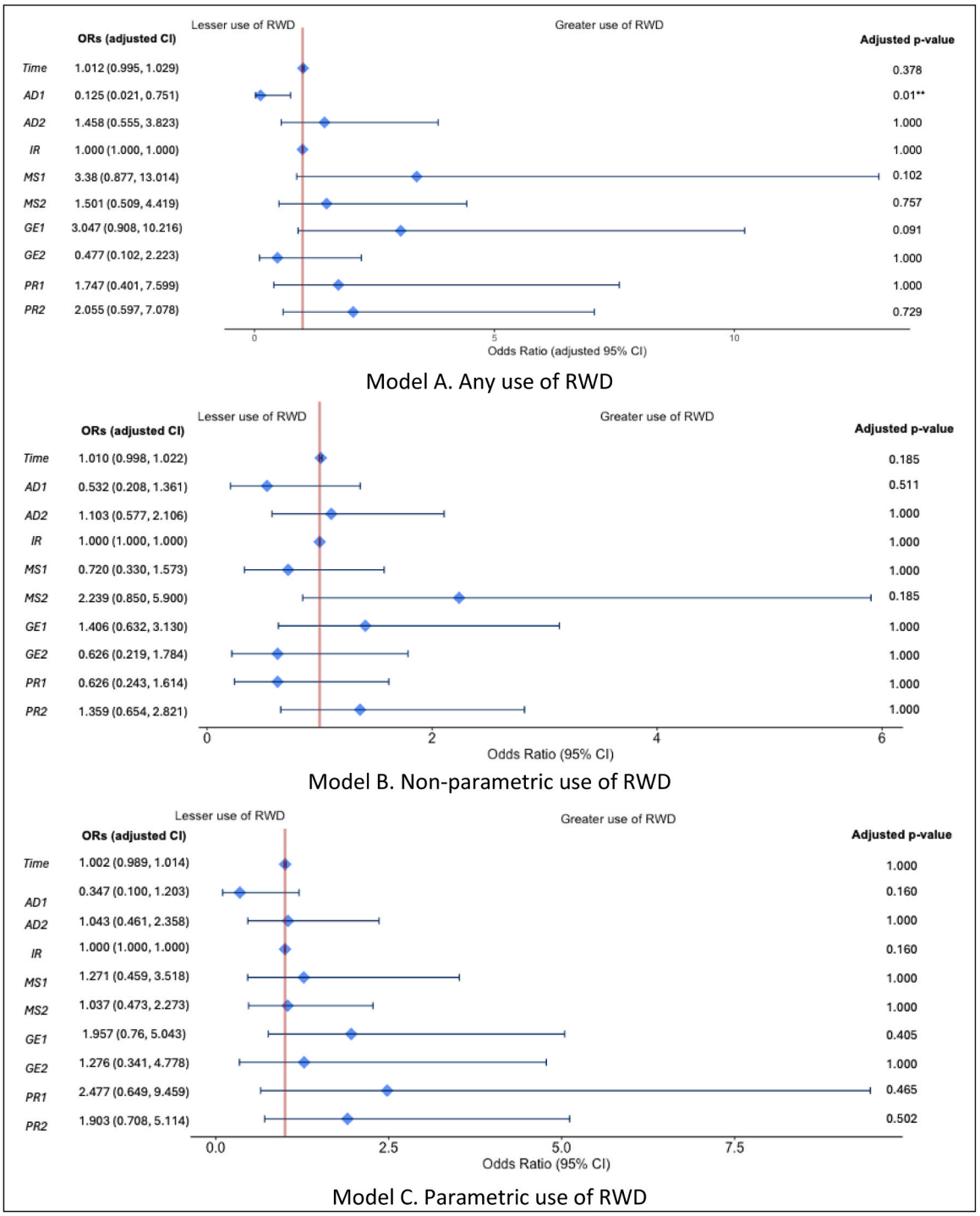

Fig. 2. Results of multivariate binary logistic models.

comparators was also found ($OR = 0.245$, *corrected CI* : $0.081 - 0.742$; *corrected* $p = 0.003$).

c. Progression free survival (PFS) for intervention and comparators

Time had a statistical association with the use of RWD in estimating PFS for intervention ($OR = 1.020$, *corrected CI* : $1.000 - 1.040$; *corrected* $p = 0.044$) whereas there was no association with estimating PFS for comparators. *AD1* had a negative association with the use of RWD in estimation of PFS for comparators ($OR = 0.159$, *corrected CI* : $0.041 - 0.616$; *corrected* $p = 0.001$).

d. Transition probability

Time had a statistical association with the use of RWD in estimation of transition probability ($OR = 1.040$, *corrected CI* : $1.001 - 1.081$; *corrected* $p = 0.035$). The logistic regression result also showed that *PR2* had a positive association with the use of RWD in estimating transition probabilities ($OR = 7.984$, *corrected CI* : $1.278 - 49.899$; $p = 0.013$).

4. Discussion

This study used binary logistic regression analyses to investigate the factors associated with greater or lesser use of RWD in economic

modelling. The key identifying feature of the selected explanatory variables is that they may be related to potential evidence gaps or the availability of suitable RWD in drug appraisals. A few studies have reviewed the potential use of RWD in HTA and highlighted the application of RWD in some situations, such as understanding the impact of new health technology when RCTs are not available [22]. However, there is limited understanding of when greater or lesser use has been made of RWD. This is the first study to test hypotheses with respect to the use of RWD in economic modelling for HTA based on data systematically extracted from NICE STA guidance issued over twelve years. Beyond documentation of the previous use of RWD, this study can contribute to systematic understanding of use of RWD by analysing the associations with use of RWD in economic modelling for drug appraisals.

The primary explanatory variable, *Time* and primary outcome variable, *any* use of RWD were not associated. However, *Time* was associated with the use of RWD for validating the survival distribution of the intervention and for estimation of OS for comparators. Notably, in many appraisals, RWD have been used to support the choice of survival distribution for the clinical outcome, and to estimate survival outcome for comparator arms in recent appraisals. Over time, these two areas have been particularly highlighted when discussing the use of RWD [23–25]. This result implies increasing interest in use of RWD. Increasing use of RWD in recent appraisals could be, in part, a result of the NICE Decision Support Unit (DSU) recommendation that external data should be used to assess the clinical plausibility of survival curves [26], and practical guidance on how to use observational data to estimate treatment effectiveness [27]. However, it is difficult to distinguish the impact of the DSU recommendation from the trend for increased use of RWD over time. The NICE real-world evidence framework, published in 2022, provides guidance on the use of RWD. This framework especially highlights methods for real-world studies of comparative effects. Given the trend of increasing interest in RWD, this guidance may lead to more systematic use of RWD in future TA guidance. A future study with further data collection is required to help understand the impact of NICE guidance on use of RWD in TA guidance.

Any use of RWD had negative associations with availability of direct treatment comparisons for all or some comparators (*AD1*). HTA decision-making requires an assessment of new technology comparing technologies currently being used. When a direct comparison was not made in a RCT, external sources, including RWD, are likely to be used to compare clinical and cost-effectiveness. Absence of direct comparison becomes more critical when it comes to estimating survival benefit in the assessment. Indirect comparison must be made to assess the new technology, providing opportunities for RWD to be used in estimating survival outcome for comparators. This study found that the *AD1* variable was associated with use of RWD for estimating OS for comparators. Regardless of data type, suitable data, for example, data in the relevant population for the decision problem, are required in the model when an RCT fails to provide the information about the comparators. This finding is aligned with the current trend of using RWD in external control arms [11,28,29]. In a separate study, whether single-arm trial or availability of trial data for comparator have impact on the use of RWD in estimating OS for comparators would be explored with further analysis.

PR2 was positively associated with the use of RWD for validating survival curve for comparators and estimating transition probabilities. This hypothesis assumed that data from routine clinical practice would be more likely to be available if the technology was already recommended for routine commissioning or use within cancer drugs fund (CDF) for other indications. Although statistical association with *PR2* was only found with these two outcome variables, some CDF review appraisals used RWD from the systematic anti-cancer therapy dataset for their re-appraisals. However, the impact of RWD for these data is unclear [30]. When it comes to estimating transition probabilities, this association was found for a different reason. Previous guidance or literature were frequently used to estimate transition probability between stages, for example, loco-regional recurrence rate to metastasis in a Markov model. While partitioned survival models are more common in cancer appraisals, the Markov model was used in some appraisals, such as blood cancers. As these appraisals are similar in terms of nature of disease, the same observational studies were frequently used across appraisals. The association between *PR* and estimating transition probability appears because the same observational study is repeatedly used for certain Markov stages, rather than new data becoming available after a drug is introduced.

No statistical association was found between use of RWD and *GE*. This may result from the different levels of generalisbility being poorly distinguished. *Moderate GE* was recorded in more than half of STAs whereas *questionable GE* was recorded in only 15 % of appraisals. This study tried to distinguish different levels of *EV*. However, this was challenging due to the different expressions used across appraisals to indicate concerns over generalisability. Information about the generalisability of clinical trials was extracted from the ERG reports. Several different ERGs participate in the NICE appraisal process. Although these external groups strictly follow the guidance on the critical review, variation in the focus areas has been reported [31]. The assessment of generalisability is one of the areas where differences are often found. Comments on uncertainty regarding generalisability made by the ERGs might not be comparable due to the different language used and different perspectives taken by ERGs across appraisals. The differences in reporting may contribute to the lack of statistical significance and is one of the limitations of this study.

It was anticipated that economic models of treatments for rare cancers would use more RWD due to difficulties conducting RCTs [32]. However, the expected association with incidence rate was not found. The stakeholder interviews potentially can provide some insight into this result [17]. During these interviews, the rareness of a disease was identified as a negative factor in the collection of meaningful RWD for appraisals. The number of patients in registries of rare cancers was not usually enough for drug appraisals. Also, a large proportion of the rare cancer patients might already be included in the clinical trials of treatments. Thus, rarity may be associated with greater reliance on clinical trial data rather than registry data.

The correlation analysis between variables identified that *Risk of bias (RB)* was collinear with other variables. The information about *RB* was extracted from 'Quality assessment of the relevant clinical effectiveness evidence' in the Evidence Review Group (ERG) reports. ERGs usually use a tool for risk of bias assessment recommended by NICE when assessing the internal validity of clinical trials [33]. The criteria include randomisation, concealment of treatment allocation, selective reporting, and completeness of reporting of outcomes. These criteria are, to some extent, related to the explanatory variables used in this study. For example, appraisals using single-arm clinical trials as the main clinical evidence are reported as having a high risk of bias due to the absence of double blinding and randomisation. While various criteria are usually used to evaluate the internal validity for non-randomised clinical evidence, this study regarded single-arm clinical trials as having a high risk of bias due to the absence of randomisation. As the *RB* had the highest correlation, this variable was excluded for the analysis to reduce multicollinearity. While the highly correlated variable *RB* was excluded, two variables *IR* and *MS* showing some correlations with other variables were retained in the regression model as they were less highly correlated than *RB*. This study has highlighted the statistical significance rather than the estimates of the regression coefficients as multicollinearity less likely influence the sign of the coefficient [34] while regression coefficients become unstable and difficult to interpret due to increasing standard error. Instead of excluding all correlated variables, excluding only the highly correlated variables can have a benefit of not losing many independent variables.

There can be other factors which are potentially associated with use of RWD. Although the explanatory variables in the logistic regression covered most situations where additional data are required or where additional data are available in economic models, other factors might be

influential in the use of RWD. For instance, companies can be incentivised to use more RWD due to their market access strategy. Also, some manufacturers could be more confident than others to use more RWD in appraisals. Such factors were not considered in this analysis.

Another limitation of this paper is to count all use of RWD, regardless of intensity of use of RWD. The intensity of using RWD is one way to measure the impact of its use by considering whether a particular use of RWD or combination of use (pattern of use) can potentially have larger impact than some other types of uses. This study has not taken account of intensity of use of RWD when exploring the hypotheses about the use of RWD. All uses were considered equally important whereas all uses have different impacts in the economic modelling. This paper presented the results of a simpler analysis where all uses of RWD are considered equally relevant, prior to analyses recognising that this may not be the case. A follow-up study will investigate how intensively RWD were used in appraisals and what factors were associated with increased intensity of use of RWD.

This is the first study to assess associations between use of RWD and a range of factors in economic models in NICE STAs of oncology medicines. While previous studies investigated the use of RWD in fewer appraisals without reporting how use of RWD was extracted or tried to identify use of RWD from stakeholder interviews, this study investigated statistically the association with use of RWD using data systematically extracted from 267 appraisals following a protocol. The statistical analysis of factors associated with increased use of RWD can provide a clearer picture of where and why RWD have been used, compared with simple description.

5. Conclusion

RWD were more likely to be used in economic modelling of cancer drugs when randomised controlled trials failed to provide relevant clinical information of the drug for appraisals, particularly in the absence of direct treatment comparisons. These results, based on analysis of data systematically collected from previous appraisals, suggest that uses of RWD were associated with data gaps in the economic modelling. While this result may support some of the advantages of using RWD when evidence is absence, the question, to what extent has the use of RWD for indirect treatment comparison reduced uncertainty in decision-making remains to be answered.

Ethics approval

This study was approved by the Ethics Committee of the London School of Hygiene and Tropical Medicine on 14 November 2019 (17315).

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John Cairns is a diagnostic advisory committee member of the National Institute for Health and Care Excellence.

Role of the funder/sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Also, any fellowship or external contribution had impacts on this paper.

Author contributions

Both authors contributed to conceptualising and designing the study. JK (the guarantor) contributed to acquisition of the data and data analyses. JK and JC contributed to interpretation of the data. JK wrote the original version of the manuscript. JC contributed to the critical revision of the manuscript. JK has full responsibility for the work and conduct of the study.

Informed consent

Not applicable.

CRediT authorship contribution statement

John Cairns: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Jiyeon Kang:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jiyeon Kang is supported by the Centre for Cancer Biomarkers, University of Bergen, funded by the Research Council of Norway grant number (223250). She also holds a ESRC (Economic and Social Research Council) postdoctoral fellowship. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Also, any fellowship or external contribution had no impacts on this paper.

John Cairns is a diagnostic advisory committee member of the National Institute for Health and Care Excellence.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jcpo.2024.100507.

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