THE INCREASING USE OF POPULATION-ADJUSTED INDIRECT COMPARISONS IN THE NICE HEALTH TECHNOLOGY ASSESSMENT (HTA) SUBMISSION PROCESS AND THE RESPONSE TO THESE METHODS

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BACKGROUND

- The comparative efficacy and safety of new interventions relative to standard of care is necessary to establish during the health technology assessment process. However, new interventions often do not have a direct trial comparing its efficacy and safety with all relevant comparators.
- In such situations, indirect comparisons can be used to generate estimates and are often central to establishing the efficacy and safety estimates used in the HTA process.
- While traditional network meta-analysis (NMA) is considered the gold standard when performing indirect comparisons, it is not always possible. They rely upon forming a network of comparable randomised controlled trials (RCTs) with at least one shared comparator being present in each trial.
- RCTs may not be considered to be comparable due to differences in study design or patient populations. They may not have a shared comparator which would allow a network to be formed. Additionally, many submissions for early access medicines are based on phase II single arm trials rather than RCTs.
- In cases where traditional NMA is not possible alternative statistical approaches such as matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) have been used (**Figure 1**).
- These alternative statistical methods tend to result in models with greater uncertainty than traditional NMA but allow comparison in situations where there is a paucity of clinical trials.

OBJECTIVE

- We reviewed technology appraisals (TAs) from the National Institute for Health and Care Excellence (NICE) to assess how the use and acceptance of different approaches to indirect comparison have changed over time.

METHODS

- A systematic search was performed of the NICE website for TAs which included a MAIC or STC
- The following search terms were used:
  - matched adjusted
  - matching adjusted
  - MAIC
  - simulated treatment
  - STC
  - adjusted indirect
- The statistical methods, clinical evidence, assessments and recommendations were extracted and summarised.

RESULTS

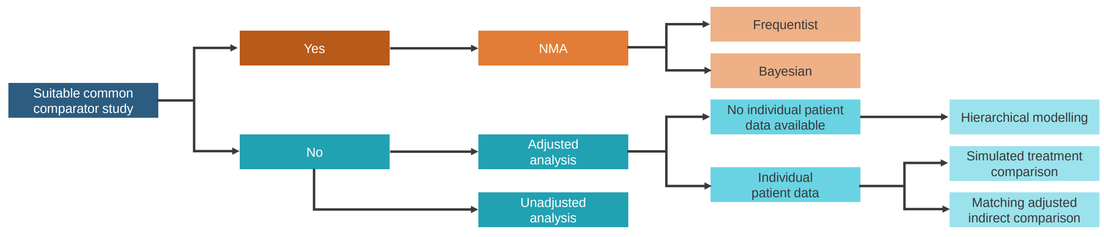
Overview of approaches

- Thirty-six TAs were identified on the NICE website:
  - 49 included a MAIC (published 2014–2022)
  - 7 included an STC (published 2015–2021)

Change over time

- Use of the MAIC approach has increased over time; particularly in the years 2021-22 (**Table 1, Figure 2**).
- The use of STCs is also recent with three of the four TAs published from 2017 onwards, however there is not sign of their use increasing over time.
- Both MAIC and STC approaches have mainly been used in oncology (47/54 TAs).
- Prior to 2017, the 4 MAICs and 1 STC published were used to either adjust for differences between comparative trials or to allow comparative trials without a common comparator to be compared.
- Since 2017 onwards, thirty one of forty-seven MAICs and/or STCs performed have been used to allow single arm trials to be compared to other trials.

Figure 1. Potential methodologies with which to perform an indirect comparison



NICE review of approaches

- There was a mixed response from NICE regarding the use of these alternative indirect comparisons.
- Indirect comparisons were responded to on a case-by-case basis, and it was often felt that they introduced additional uncertainty.
- NICE will often reject the findings of the alternative approach; however, they will still factor the results into their decision-making in situations where data are scarce.
- NICE decisions on these submissions often included a managed access agreement necessitating the collection of additional data.

Figure 2. The number of MAICs and STCs used in NICE submission published between 2014-2022

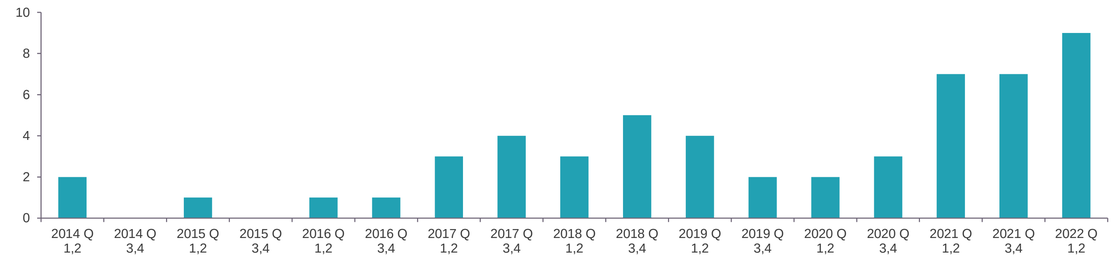


Table 1. Description of the which approach was used, why the approach was required, and the reception given by NICE to the analysis

Title	Condition type	MAIC	STC	Comparative trial: intervention	Date	Reason	Response to MAIC or STC	Recommended	Agreement	End of life criteria met	CDF
Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis (TA308)	Inflammatory	1		yes	26-Mar-14	Not reported	Suggested the approach	yes	no	no	NA
Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311)	Oncology	1		yes	23-Apr-14	No common comparator	Accepted company MAIC	yes	no	no	no
Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (TA333)	Oncology		1	yes	25-Feb-15	No common comparator	Accepted company MAIC	yes	PAS	In some population groups	no
Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380)	Oncology	1		yes	27-Jan-16	Adjust for study differences	Accepted company MAIC	yes	PAS	no	no
Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (TA426)	Oncology	1		yes	21-Dec-16	Not reported	Not accepted	yes	PAS	no	Yes
Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427)	Oncology	1		yes	11-Jan-17	No common comparator	Accepted company MAIC	yes	PAS	In some comparisons	no
Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429)	Oncology	1		yes	25-Jan-17	Adjust for study differences	Accepted company MAIC	yes	PAS	yes	no
Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451)	Oncology	1		no	28-Jun-17	Single arm data	Accepted company MAIC	yes	PAS	In some population groups	no
Carfilzomib for previously treated multiple myeloma (TA457)	Oncology	1		yes	19-Jul-17	Adjust for dosing schedule change	Accepted company MAIC	yes	PAS	no	no
Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (TA462)	Oncology	1		no	26-Jul-17	Single arm data	Accepted company MAIC	yes	CA	yes	no
Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (TA478)	Oncology	1		no	04-Oct-17	Single arm data	Not accepted	yes	CA	no	no
Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492)	Oncology	1	1	no	06-Dec-17	Single arm data	The STC was not felt to be robust and the MAIC was performed in response	yes	MAA	no	yes
Ceritinib for untreated ALK-positive non-small-cell lung cancer (TA500)	Oncology	1		yes	24-Jan-18	No common comparator	Accepted company MAIC	yes	PAS	no	no
Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510)	Oncology	1		no	14-Mar-18	Single arm data	Not accepted	yes	MAA	no	yes
Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522)	Oncology		1	no	13-Jun-18	Single arm data	Not accepted	yes	MAA	yes	yes
Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy	Oncology		1	no	04-Jul-18	Single arm data	Not accepted, uncertainty considered to be too high	no	no	yes	no
Dinutuximab beta for treating neuroblastoma (TA538)	Oncology	1		yes	22-Aug-18	No common comparator	Accepted company MAIC	yes	CA	No	no
Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours (TA539)	Oncology	1		mixed	29-Aug-18	Single arm data	Accepted assessment groups MAIC	yes	CA	yes	no
Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (TA540)	Oncology	1		no	03-Sep-18	Single arm data	Preference for naïve comparison	yes	MAA	yes	yes
Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554)	Oncology	1		no	21-Dec-18	Single arm data	Preference for naïve comparison	yes	MAA	no	yes
Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (TA561)	Oncology	1		yes	27-Feb-19	Adjust for study differences	Accepted company MAIC	yes	CA	no	no
Benralizumab for treating severe eosinophilic asthma (TA565)	Respiratory	1		yes	06-Mar-19	Adjust for study differences	Preference for NMA	yes	CA	no	NA
Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567)	Oncology	1		no	13-Mar-19	Single arm data	Preference for naïve comparison	yes	MAA	yes	yes
Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (TA571)	Oncology	1		no	20-Mar-19	Single arm data	Accepted company MAIC	yes	CA	yes	no
Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (TA592)	Oncology	1	1	no	07-Aug-19	Single arm data	Not accepted, uncertainty considered to be too high	Yes	MAA	Yes it might fulfil the end-of-life criteria, but this is uncertain	Yes
Idelalisib for treating refractory follicular lymphoma (TA604)	Oncology	1		no	02-Oct-19	Single arm data	Not accepted, uncertainty considered to be too high	No	No	No	No
Lenalidomide with rituximab for previously treated follicular lymphoma (TA627)	Oncology	1		yes	07-Apr-20	No common comparator	Accepted company MAIC	Yes	CA	No	No
Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer (TA628)	Oncology	1		no	13-May-20	Single arm data	Not accepted, sensitivity analysis of MAIC variables needed	Yes	CA	Yes	No
Entrectinib for treating ROS1-positive advanced non small-cell lung cancer (TA643)	Oncology	1		no	12-Aug-20	Single arm data	Accepted company MAIC	Yes	CA	Yes	Yes
Carfilzomib for previously treated multiple myeloma (TA657)	Oncology	1		yes	18-Nov-20	Adjusting population from a separate trial	Accepted company MAIC	Yes	CA	No	No
Siponimod for treating secondary progressive multiple sclerosis (TA656)	Oncology	1		yes	18-Nov-20	Adjust for differences between RCTs	Accepted company MAIC	Yes	CA	No	No
Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor (TA670)	Oncology	1		yes	27-Jan-21	Adjusting population from a separate trial	Not accepted, sensitivity analysis of MAIC variables needed	Yes	CA	NA	No
Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (TA673)	Oncology		1	yes	17-Feb-21	Adjusting population from a separate trial	Not accepted, uncertainty considered to be too high	Yes	MAA	No	Yes
Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma (TA677)	Oncology	1		no	24-Feb-21	Single arm data	Accepted company MAIC	Yes	MAA	Yes	Yes
Dapagliflozin for treating chronic heart failure with reduced ejection fraction (TA679)	Cardiovascular	1		yes	24-Feb-21	Unclear	Not accepted, no justification for doing a MAIC	Yes	No	No	No
Acalabrutinib for treating chronic lymphocytic leukaemia (TA689)	Oncology	1		yes	21-Apr-21	No common comparator	Accepted company MAIC	Yes	CA	No	No
Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (TA695)	Oncology	1		yes	28-Apr-21	No common comparator	No need for comparison	Yes	CA	No	No
Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (TA704)	Oncology	1		no	26-May-21	Single arm data	Not accepted, uncertainty considered to be too high	Yes	MAA	Yes	Yes
Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716)	Oncology	1		no	28-Jul-21	Single arm data	Not accepted, uncertainty considered to be too high	Yes	CA	Yes	No
Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722)	Oncology	1		no	25-Aug-21	Single arm data	Not accepted, uncertainty considered to be too high	Yes	CA	Yes	Yes
Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable (TA739)	Oncology		1	no	27-Oct-21	Single arm data	Accepted company STC	Yes	CA	Yes	No
Selpercatinib for treating advanced thyroid cancer with RET alterations (TA742)	Oncology	1		no	03-Nov-21	Single arm data	Not accepted, uncertainty considered to be too high	Yes	MAA	No (Selpercatinib does not meet the end-of-life criteria for both populations but the data is highly uncertain)	Yes
Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA752)	Inflammatory	1		yes	15-Dec-21	Single arm extension study data	Not accepted, uncertainty considered to be too high	Yes	CA	No	No
Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA756)	Oncology	1		no	16-Dec-21	Single arm data	Accepted company MAIC	Yes	MAA	No	Yes
Risdiplam for treating spinal muscular atrophy (TA755)	Genetic	1		yes	16-Dec-21	Single arm data for sub-population	Accepted company MAIC	Yes	MAA	Yes (it is reasonable to accept that risdiplam meets the short life expectancy criterion for type 1 SMA)	NA
Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (TA763)	Oncology	1		yes	02-Feb-22	No common comparator	Not accepted, uncertainty considered to be too high	Yes	CA	No	No
Dapagliflozin for treating chronic kidney disease (TA775)	CKD	1		yes	09-Mar-22	The adjuste for patient populations	Accepted company MAIC	Yes	No	No	No
Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria (TA778)	Anaemia	1		yes	09-Mar-22	The adjuste for patient populations	Not accepted, uncertainty considered to be too high	Yes	CA	No	No
Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779)	Oncology	1		no	16-Mar-22	Single arm data	Accepted company MAIC	Yes	MAA	Yes	Yes
Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (TA781)	Oncology	1		no	30-Mar-22	Single arm data	Accepted company MAIC	Yes	MAA	Yes, but the length of life extension is uncertain.	Yes
Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA783)	Oncology	1		no	13-Apr-22	Single arm data	Not accepted, insufficient adjustements made/high uncertainty	Yes	CA	Yes	Yes
Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (784)	Oncology	1		yes	20-Apr-22	Subgroup analysis	Accepted company MAIC	Yes	CA	No	Yes
Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations (789)	Oncology	1		no	18-May-22	Single arm data	Accepted updated MAIC	yes	CA	Yes	Yes
Ibrutinib for treating Waldenstrom's macroglobulinaemia (795)	Oncology	1		no	08-Jun-22	Single arm data	Rejected ERG requested MAIC, high uncertanty	No	No	No	Yes

CA, commercial arrangement; CDF, Cancer Drugs Fund; MAA, managed access agreement; MAIC, matching-adjusted treatment comparison; NMA, network meta-analysis; PAS, patient access scheme; STC, simulated treatment comparison.

CONCLUSIONS

- There has been a large increase in the use and acceptance of alternative statistical approaches to indirect comparison, most notably MAICs.
- This is likely driven by the increase in the amount of treatments having their European Medicines Agency approval accelerated and based on a single arm trial.
- The use of MAICs is becoming central in the preparation of NICE submissions where traditional NMA is not possible, particularly in the area of oncology.
- The NICE Decision Support Unit technical support document on methods for population-adjusted indirect comparisons in submissions highlights the need for standardisation for MAIC and STC approaches.
- Such standardisation is essential with the increasing use of these methodologies in NICE submissions in situations of data scarcity.

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