A Review of NICE Technology Appraisals Using Single-Arm Trials

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BACKGROUND

- Head-to-head randomized controlled trials (RCTs) remain the gold standard for establishing relative treatment efficacy and for use in cost-effectiveness (CE) models.[1-4]
- Health agencies, such as the National Institute for Health and Care Excellence (NICE), when assessing a health care technology, need to base their recommendations regarding the value of the technology on evidence, even when the evidence comes only from single-arm trials. These agencies must weigh the inherent difficulties presented by having evidence only from single-arm trials with the potential health and economic benefits of the new technology for patients and society.[1]

OBJECTIVE

- The objective of this study was to investigate the extent to which single-arm trials have been used in NICE submissions and submission models, and whether NICE has recommended drugs for which the primary evidence was from single-arm trials.

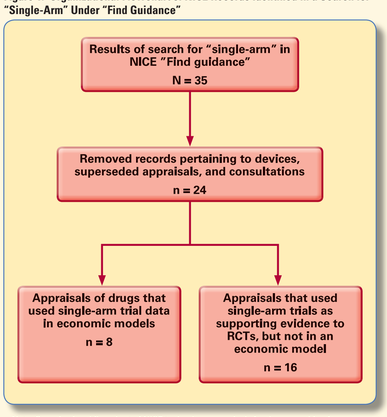
METHODS

- We searched the NICE website for completed health technology assessment (HTA) appraisals using the term "single-arm." We excluded instances of devices and superseded appraisals. Finally, we excluded appraisals in which the single-arm trial data were used only as evidence to support data from RCTs.
- We recorded the date of the appraisal, the therapeutic area, whether the single-arm trial data were used in an accompanying cost-utility model, the type of data provided by the single-arm trial (i.e., efficacy, adverse events, utilities), the NICE recommendation about the technology, and comments by the Appraisal Committee and/or the Assessment Group and/or the Evidence Review Group on the use of the single-arm trial data as the primary evidence of effectiveness.

RESULTS

- The search resulted in 35 records including a reference to "single-arm" (Figure 1). Eleven were excluded because they pertained to devices, had been superseded, or described NICE consultations. The remaining 24 appraisals for drug treatments included a reference to "single-arm."
- Sixteen appraisals provided the single-arm trial data as supporting evidence to at least one RCT.
- Eight appraisals used single-arm trial data in an accompanying economic model. Of these eight, four used the single-arm trial efficacy data as the primary evidence of effectiveness (Table 1).
- Only one of the four appraisals that used single-arm trial data as the primary evidence of effectiveness in the model resulted in a positive recommendation from NICE (Table 1).
- Because our review aimed to explore the use of single-arm trials in establishing relative effectiveness in CE models, we explored in detail the four appraisals that used single-arm trial data as the primary evidence for effectiveness in a model.

Figure 1. Organizational Flowchart of NICE Records Identified in a Search for "Single-Arm" Under "Find Guidance"



Note: Organizational flowchart of NICE technology appraisals for drugs resulting from a search of "single-arm" in the "Find guidance" search box, conducted on January 16, 2014.

T178 Advanced and/or Metastatic Renal Cell Carcinoma

- TA178 was a multiple technology appraisal involving four manufacturer submissions and the Assessment Group's evaluations of four drugs for the treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC).[5]
- The assessment of second-line sunitinib was based on evidence from two small single-arm trials (n = 63 and n = 106). Overall survival, progression-free survival, tumor response, and EuroQol 5 Dimensions (EQ-5D) data were collected in both trials. NICE did not recommend sunitinib as a second-line treatment of this population. (RCT evidence was submitted for first-line sunitinib and the other three drugs; however, these assessments were not of interest to our review.)
- The manufacturer model compared sunitinib with best supportive care (BSC) using data for each intervention from separate sources. For sunitinib, data from the smaller of the single-arm trials was used. For BSC, the submission used a pooled analysis of data from multiple sources (a review and Medicare data). Survival analysis was used to model disease progression, survival, and treatment effect, with Weibull survival curves used to extrapolate from different (and independent) sources of data.
- EQ-5D data collected during the smaller sunitinib single-arm trial were used to estimate health-state utilities depending on health state and treatment.
- The Assessment Group stated that the modeling approach was invalid given that randomization had been broken, the two data sources for BSC survival had important limitations, the single-arm trial of sunitinib was very small, and overall survival data for sunitinib from the single-arm trial were not mature. The Appraisal Committee reported that based on the lack of robust evidence of effectiveness, it could not conclude that sunitinib is an effective second-line treatment for advanced and/or metastatic RCC.

TA202 Chronic Lymphocytic Leukaemia

- TA202 was a single technology appraisal for ofatumumab for the treatment of patients with chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab. The manufacturer's economic model compared treatment with ofatumumab with BSC.[6]
- NICE did not recommend ofatumumab.
- The main source of evidence submitted by the manufacturer was a single-arm trial that included 154 patients with chronic lymphocytic leukaemia; of these 154 patients, 59 patients met the criteria for being refractory to fludarabine and alemtuzumab.
- The main source of data on the effectiveness of ofatumumab for the economic model was an interim analysis of the single-arm trial. Effectiveness estimates for ofatumumab were based on data from all 59 patients, both responders and nonresponders.
- Effectiveness estimates for BSC were based on a subgroup of 25 patients who did not respond to treatment.
- No data on median overall survival were available at the time of submission, although interim analysis seemed to indicate that there was an increase in overall survival for responders compared with nonresponders. To estimate overall survival and progression-free survival, the manufacturer fit data for each endpoint for nonresponders using a Weibull distribution. Estimates of hazard ratios for progression-free survival and overall survival for ofatumumab compared with BSC (represented by nonresponders) were calculated from a Cox proportional hazards regression. The regression analysis included covariates for age, sex, Rai score, Eastern Cooperative Oncology Group status, number of prior therapies, and time since diagnosis. The hazard ratios then were applied to the BSC Weibull survival functions to obtain overall survival and progression-free survival estimates for the ofatumumab arm.
- The main concern expressed by the Evidence Review Group and the Appraisal Committee was the use of outcomes data from a subgroup of patients who were nonresponders to treatment as the basis for effectiveness of BSC, and the use of the outcomes data from all patients as the basis for effectiveness of ofatumumab. The Appraisal Committee commented that it was not clear how this approach would bias the estimate of incremental effectiveness and expressed that it was not confident that this approach would be comparable to evaluating ofatumumab versus placebo.

TA299 Previously Treated Chronic Myeloid Leukaemia

- TA299 was a single technology appraisal of bosutinib for patients with chronic myeloid leukaemia (CML) who had been previously treated with one or more tyrosine kinase inhibitors and for whom imatinib, nilotinib, and dasatinib were not considered appropriate. The economic model compared bosutinib with hydroxycarbamide alone and with stem cell transplant for the blast and accelerate phase. For the chronic phase, the model compared bosutinib with interferon alfa.[7]
- NICE did not recommend bosutinib.
- The clinical effectiveness evidence submitted by the manufacturer was from a single-arm study of bosutinib that was not originally designed for the indicated population. The manufacturer used a subgroup of 52 patients who met the criteria for being resistant to or intolerant of imatinib.
- For the economic model, the response rate for bosutinib in the chronic phase was based on the best cumulative response rate observed in the trial. For the accelerated and blast phase cohorts, the model used an exponential distribution to estimate overall survival from the trial data. The manufacturer's rationale for the two separate approaches was that the estimates for survival for the chronic phase populations were not yet available, and therefore, that analysis would require significant extrapolation, whereas overall survival data for the accelerated and blast phase populations were available, requiring less extrapolation. For the chronic phase, the model assumed a surrogate relationship between major cytogenetic response and overall survival, and time off treatment with bosutinib was calculated by subtracting time on treatment from the estimated overall survival. These assumptions led to a considerable posttreatment effect with bosutinib.
- For the comparators, overall estimates of survival were obtained from three previous published single-arm studies. To estimate effectiveness in the model, subgroup populations that met the criteria for the bosutinib indication were included from these trials. An indirect comparison was used to obtain the relative effectiveness in the model.
- The Appraisal Committee and the Evidence Review Group expressed concern because the evidence of clinical effectiveness for both bosutinib and the comparator treatments were from single-arm studies. The Evidence Review Group noted that patients in the comparator studies seemed to be younger than the patients in the bosutinib study. Moreover, the Evidence Review Group described the comparison of the single-arm bosutinib study with the nonrandomized comparator studies as being strongly susceptible to bias.

TA300 Chronic Hepatitis C in Children and Young People

- TA300 was a multiple technology assessment including two manufacturers' submissions and the Assessment Group's evaluation of peginterferon alfa-2a and peginterferon alfa-2b (both plus ribavirin) for treating chronic hepatitis C in children and young people. The models compared treatment with peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin with BSC.[8]
- Although the Appraisal Committee recognized that comparative evidence was lacking, NICE recommended peginterferon alfa (2a and 2b) in combination with ribavirin for children and young adults to treat chronic hepatitis C.
- The manufacturer's model for peginterferon alfa-2a plus ribavirin applied clinical effectiveness estimates based on the weighted average of patients from one arm of the RCT and three single-arm studies.
- The manufacturer's model for peginterferon alfa-2b plus ribavirin applied clinical effectiveness estimates based on the weighted average of patients who had sustained virological response from eight single-arm trials.
- The Assessment Group's model evaluated peginterferon alfa-2a and 2b. For the clinical effectiveness for peginterferon alfa-2a, it applied estimates based on one arm of an RCT and one single-arm study; for peginterferon alfa-2b, it applied estimates based on five single-arm trials.
- Although the Assessment Group commented that the quality of the studies was poor, due to the lack of a control group and inconsistent patient inclusion criteria, it considered several other factors in the recommendation:
  - The two manufacturers' models and the Assessment Group's model all demonstrated the intervention to be dominant over standard care.
  - Treatment with peginterferon alfa could provide a sustained virological response that could potentially last for the lifetime of the child or young person, effectively providing a cure.
  - Treatment with peginterferon alfa could provide benefits to parents and caregivers, including reducing the guilt burden associated with maternal transmission of hepatitis C.
  - Treatment with peginterferon alfa in young children could help avoid the social stigma associated with hepatitis C infection.
- Several additional factors may have been influential in the positive recommendation:
  - Clinical evidence was presented from one arm of an RCT and six additional single-arm trials.
  - There is no other treatment for chronic hepatitis C licensed for children and young people in the United Kingdom.
  - Treatment was already in use; therefore, withdrawing it would remove the only available treatment for these patients.

Table 1. HTA Appraisals Using Single-Arm Trial Data in Economic Models

Number	Date	Disease Area	Use of Single-Arm Trial Data				Recommended
			Efficacy	Utilities	Adverse Events	Extension to RCT	
1. TA178	26 Aug 2009	Renal cell carcinoma	x	x			No
2. TA202	27 Oct 2010	Chronic lymphocytic leukemia	x		x		No
3. TA211	15 Dec 2010	Chronic constipation			x		Yes
4. TA214	23 Feb 2011	Breast cancer				x	No
5. TA247	22 Feb 2012	Rheumatoid arthritis				x	Yes
6. TA255	11 May 2012	Prostate cancer		x			No
7. TA299	27 Nov 2013	Chronic myeloid leukemia	x	x	x		No
8. TA300	27 Nov 2013	Hepatitis C	x				Yes

CONCLUSIONS

- Randomized controlled trials are preferred for relative efficacy data for use in cost-effectiveness analyses in NICE HTA appraisals.
- There is one case of a positive NICE recommendation where efficacy evidence was based on single-arm trials. In this case, the clinical efficacy used in the CE model was based on multiple single-arm trials, the model results from the three manufacturers and the Assessment Group all demonstrated dominance, there was a lack of an alternative treatment option, and there were significant potential benefits of the treatment to patients and caregivers.
- Based on this review, drugs are unlikely to be approved by NICE on the basis of single-arm trial evidence (where used as the primary source of efficacy evidence) unless there is substantial supporting evidence from other sources (e.g., multiple single-arm trials) and/or unless there are other factors (e.g., high burden and unmet need).

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