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Implementing NICE guidance for evidence synthesis in technology appraisals: An overview of common methodological and analytic challenges.

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Purpose and objective

- Recent guidance on appraisal methods provides a clear framework for establishing the clinical and cost-effectiveness of technologies[1]. These approaches present three main challenges:

1. All relevant/feasible interventions and comparators should be included
2. The evidence must be complete and fit for the purpose
3. Evidence should be synthesised in an appropriate manner.

- A recent review of the clinical and cost-effectiveness of docetaxel plus prednisone for metastatic hormone refractory prostate cancer (mHRPC) is presented as a case-study.
- Emphasis is given to overall survival for docetaxel plus prednisone 3-weekly & prednisone alone (the licensed treatments for mHRPC in the UK).

APPROACHES USED

Including all relevant comparators

- All relevant and feasible alternative interventions for the patient group of interest need to be compared.
- Initial scoping did not identify any direct (head-to-head) evidence for a number of the specified comparators.
- A broader search was undertaken to identify possible direct and indirect comparisons, to complete the evidence network for docetaxel plus prednisone.

Completing the evidence

- The most appropriate measures of treatment effect for time-to-event data in a meta-analysis are hazard ratios (HR) as these measures allow for censoring.
- Survival data were reported inconsistently between trials.
- Using the method outlined by Parmar[2] hazard ratios with 95% confidence intervals (CI) were estimated, if not directly reported using the following hierarchy of evidence:

1. HR and number of events
2. Number of events and p-value
3. Survival curve with length of follow-up

Synthesising the evidence

- All evidence synthesis must be appropriate and statistically robust.
- As the evidence network was incomplete, indirect comparisons were necessary.
- Using the method proposed by Bucher[3], adjusted indirect comparisons were performed to compare the efficacy of docetaxel plus prednisone versus prednisone alone.
- Using this method maintains the power of randomisation in the original studies. This method is only valid when the magnitude of the treatment effect is consistent between the different studies being compared.
- The internal validity of the trials must be considered, with respect to the similarity of the patient populations and treatment regimens.

Lessons learnt

- There is a case for extending the evidence network and broadening the search strategy so that all relevant evidence is incorporated.
- Emphasis should be placed on the most clinically appropriate outcomes, e.g. overall survival. Data must be extracted to allow for appropriate synthesis methods.
- Analysis should be based on robust statistical techniques.

RESULTS

- The scoping search identified one study, (TAX 327) providing direct evidence on docetaxel plus prednisone versus mitoxantrone plus prednisone.
- Broader searches identified additional RCTs providing indirect evidence for docetaxel plus prednisone and other relevant comparators e.g. prednisone

	Interventions		
Trial	Docetaxel + Prednisone	Mitoxantrone + Prednisone	Prednisone
TAX 327	✓	✓	
Berry		✓	✓
CCI NOV22		✓	✓
CALGB9182		✓	✓

- One study (TAX 327) reported the HR and 95% CI for overall survival.
- Estimation of the HR and 95% CI was necessary for the remaining 3 trials identified.

Trial	Hazard Ratio*	95 % CI	How derived
TAX 327 (D+P vs. M+P)	0.76	0.62 to 0.94	Reported directly
Berry et al. (M+P vs. P)	1.13	0.75 to 1.70	From p-value and number of events
CCI-NOV22 (M+P vs. P)	0.91	0.69 to 1.19	From survival curve
CALGB9182 (M+P vs. P)	1.05	0.74 to 1.49	From p-value and number of events

*HR<1 favours the intervention.

- A formal indirect comparison between docetaxel plus prednisone versus prednisone alone was undertaken, using the following formulae:

$$\text{Log}(HR_{D+P vs. P}) = \log(HR_{D+P vs. M+P}) - \log(HR_{P vs. M+P})$$

$$SE[\log(HR_{D+P vs. P})] = \sqrt{(SE[\log(HR_{D+P vs. M+P})] + SE[\log(HR_{P vs. M+P})])}$$

- The treatment regimens were similar across the trials. The populations; men with mHRPC fit enough to receive chemotherapy were assumed to be relatively homogeneous.

Comparison	HR	95 % CI
D+P vs. M+P	0.76	0.62 to 0.94
M+P vs. P*	0.99	0.82 to 1.20
D+P vs. P	0.75	0.57 to 0.999

*Pooled analysis of the 3 trials

Conclusions

- Current guidance presents a number of methodological and technical challenges. This review demonstrates how formal approaches can be used to overcome these challenges and implement the current guidance.
- Various statistically robust techniques can be used to address the issues to ensure that decisions are based on complete rather than partial analyses.
- It must be acknowledged that there are logistical implications if using these methods in the future; (e.g. defining networks in advance, additional searching to ensure that potential bias is not introduced by selectively extending an evidence network).
- Consideration should be given to the generalisability of results derived indirectly.

References

1. NICE, Guide to the Methods of Technology Appraisal, 2003.
2. Parmar M et al. Extracting Summary Statistics to perform meta-analyses of the published literature for survival endpoints. Statist. Med. 1998;17:2815-2834.
3. Bucher H et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J. Clin Epidemiol. 1997;50:683-691.