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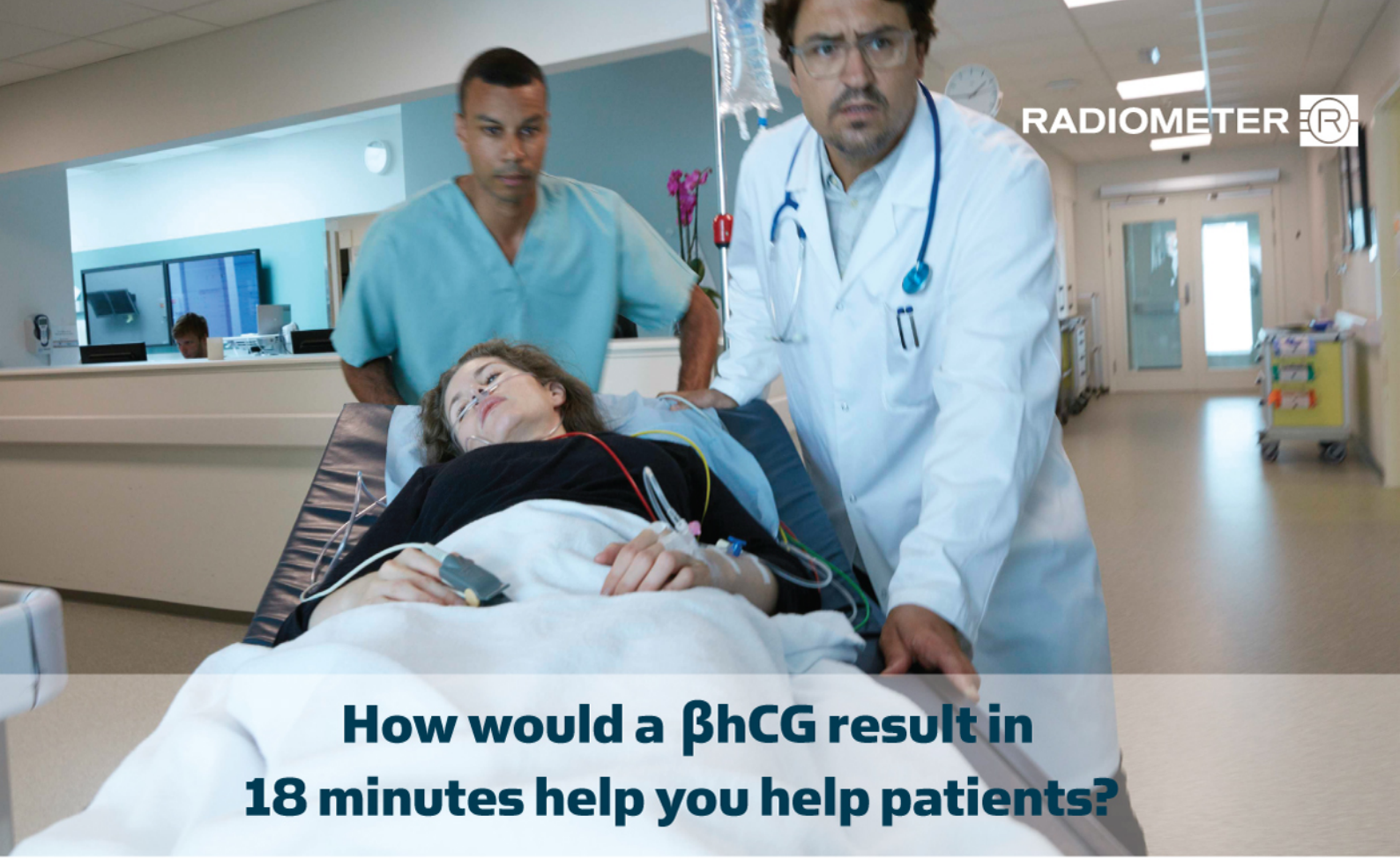

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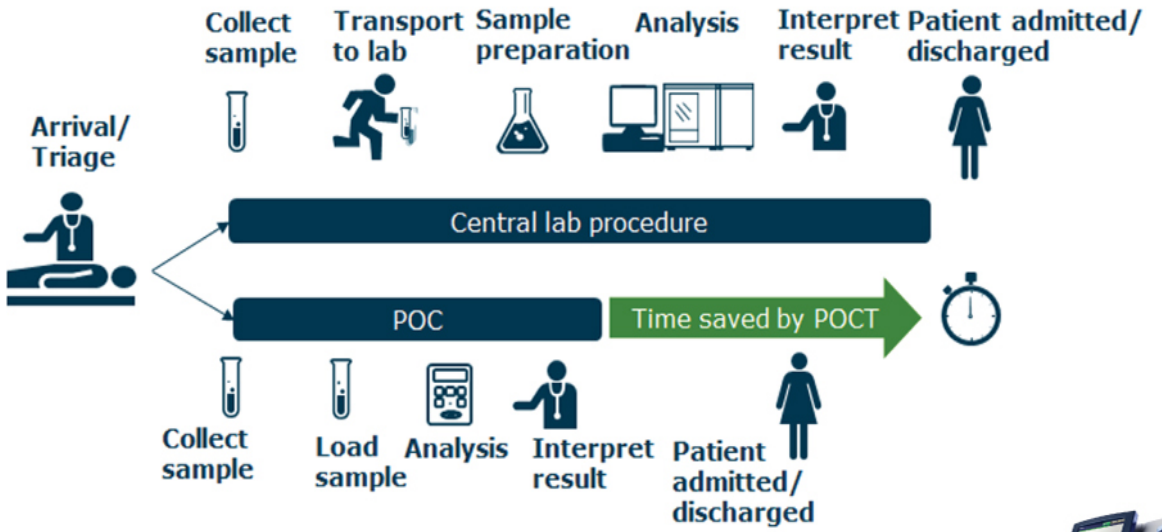

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1. Nørgaard B, Mogensen CB. Blood sample tube transportation system versus point of care technology in an ED; effect on time from collection to reporting? A randomized trial. SJTREM 2012; 20: 71.
2. Renaud B *et al*. Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes. Acad Emerg 2008; 15:216-24
3. Larsson A. *et al*; The state of point of care testing: a european perspective; Ups J Med Sci. 2015 Mar; 120(1): 1-10
4. Von Eiff W. *et al*. POCT-Management. Klinische und Ökonomische Effekte. Heidelberg: Medhochswei verlag, 2013: 189-192.

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Cost-effectiveness of mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage: an economic evaluation based on the MifeMiso trial

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Objective To assess the cost-effectiveness of mifepristone and misoprostol (MifeMiso) compared with misoprostol only for the medical management of a missed miscarriage.

Design Within-trial economic evaluation and model-based analysis to set the findings in the context of the wider economic evidence for a range of comparators. Incremental costs and outcomes were calculated using nonparametric bootstrapping and reported using cost-effectiveness acceptability curves. Analyses were performed from the perspective of the UK's National Health Service (NHS).

Setting Twenty-eight UK NHS early pregnancy units.

Sample A cohort of 711 women aged 16–39 years with ultrasound evidence of a missed miscarriage.

Methods Treatment with mifepristone and misoprostol or with matched placebo and misoprostol tablets.

Main outcome measures Cost per additional successfully managed miscarriage and quality-adjusted life years (QALYs).

Results For the within-trial analysis, MifeMiso intervention resulted in an absolute effect difference of 6.6% (95% CI 0.7–12.5%) per successfully managed miscarriage and a QALYs difference of 0.04% (95% CI −0.01 to 0.1%). The average cost per successfully managed miscarriage was lower in the MifeMiso arm than in the placebo and misoprostol arm, with a cost saving of £182 (95% CI £26–£338). Hence, the MifeMiso intervention dominated the use of misoprostol alone. The model-based analysis

Trial Registration: ISRCTN 17405024.

showed that the MifeMiso intervention is preferable, compared with expectant management, and this is the current medical management strategy. However, the model-based evidence suggests that the intervention is a less effective but less costly strategy than surgical management.

Conclusions The within-trial analysis found that based on cost-effectiveness grounds, the MifeMiso intervention is likely to be recommended by decision makers for the medical management of women presenting with a missed miscarriage.

Keywords Cost-effectiveness, cost utility, economic evaluation, management, miscarriage, model.

Tweetable abstract The combination of mifepristone and misoprostol is more effective and less costly than misoprostol alone for the management of missed miscarriages.

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Introduction

Miscarriage is a common adverse outcome of pregnancy,[1,2] with around 25% of pregnancies ending in miscarriage.[3] Miscarriage can cause harmful clinical and psychological effects as well as substantial economic impact, with an estimated annual cost of £81 million to the UK's National Health Service (NHS).[4,5] There are different types of miscarriages, with two types, missed miscarriage and incomplete miscarriage, requiring intervention.[6] A missed miscarriage is diagnosed when there is ultrasound identification of a non-viable pregnancy within the first 14 weeks of gestation.[7] A missed miscarriage can be asymptomatic and, typically, all pregnancy tissue is retained in the uterus. In contrast, an incomplete miscarriage is diagnosed when pregnancy tissue has been partly expelled by the uterus already. The management of miscarriage can be expectant (by waiting for natural expulsion), medical (treated with drugs) or surgical.

Before the publication of the 2012 National Institute for Health and Care Excellence (NICE) guidelines on 'Ectopic Pregnancy and Miscarriage' (Clinical Guidance 154),[5,8] the practice for medical management was the use of a combination of mifepristone and misoprostol. However, the NICE 2012 guidelines recommended the use of misoprostol alone, albeit based on minimal evidence.[5,9] The MifeMiso trial was conducted to assess the effectiveness and cost-effectiveness of a combination of mifepristone and misoprostol (MifeMiso) compared with misoprostol only for the medical management of a missed miscarriage.[7]

This article reports the economic evaluation conducted alongside the MifeMiso trial.[6] The primary evaluation was a within-trial cost-effectiveness analysis (CEA) based on the outcomes of cost per successfully managed miscarriage and cost per quality-adjusted life years (QALYs) gained. Additionally, a decision-analytic model was developed to assess the cost-effectiveness of the medical management of missed miscarriage with mifepristone plus misoprostol (as explored in the trial), compared with alternative strategies beyond the trial comparisons, including surgical and expectant management and the current practice of medical management, based on available secondary sources.

Methods

Design and participants

The MifeMiso trial is a multicentre, double-blinded, placebo-controlled, randomised trial. Details of the trial design and results are published elsewhere.[7] Briefly, 711 women with ultrasound evidence of a missed miscarriage were recruited from 28 hospitals across the UK, between October 2017 and July 2019.[7] The inclusion and exclusion criteria are available in Appendix S1.

Participants were randomly assigned with a one-to-one ratio to either the intervention or the placebo alternative strategy. In the intervention arm of the trial, mifepristone (Mifegyne®, single oral dose of 200 mg) followed by misoprostol (single oral, vaginal or sublingual dose of 800 microgram) 2 days later was prescribed. In the comparator arm, an identical mifepristone placebo tablet was administered, followed by a single dose of misoprostol (oral, vaginal or sublingual) 2 days later. The primary outcome for the trial was a failure to spontaneously pass the gestational sac within 7 days after randomisation.

Economic evaluation

Within-trial economic evaluation

The primary economic evaluation took the form of a CEA comparing the MifeMiso intervention versus the placebo and misoprostol combination. The analysis was based on the primary outcome of the trial and was reported in terms of cost per successfully managed miscarriage. A cost–utility analysis (CUA) was also carried out based on the

additional cost per QALY gained as a result of treatment as recommended by NICE.[10]

Model-based economic evaluation

A decision-analytic model was constructed in TREEAGE PRO 2020 and parameterised using evidence from the trial to represent the MifeMiso intervention.[11] Other comparator pathways in the model were informed by a systematic review of clinical effectiveness, conducted as part of the MifeMiso study,[12] data from a pragmatic review of economic evaluations on early miscarriage management, a UK survey performed by the MifeMiso study team, other published literature and expert opinion from within the research team (Table S1). The model, as far as possible, was constructed to represent the range of practices followed in the UK in the event of a missed miscarriage.

Details of the model pathways are presented in Appendix S2. The model structure is presented in Figure 1. Briefly, the model commences in the first 14 weeks of pregnancy after a diagnosis of missed miscarriage. Women can receive one of four alternative strategies: surgical management, expectant management, current medical management or medical management with mifepristone plus misoprostol (the MifeMiso intervention).

Data collection

Within-trial economic evaluation

Resource use and outcomes data were collected during the trial using researcher-recorded trial collection forms. Resource-use data included specified categories from randomisation until discharge from care in the Early Pregnancy Unit (EPU). The main resource categories were: (i) the quantity of medication; and (ii) the management of miscarriage, including the number of outpatient visits, emergency visits and hospital admissions until discharge (if surgery is needed to resolve the miscarriage).

Unit costs (Table 1) were identified from established national sources, with weighted averages applied when appropriate.[13,14] All costs are expressed in 2019–20 UK pounds Sterling and costs from earlier years were inflated using the NHS cost inflation index (NHSCII).[14]

For the medications, as all participants received an initial dose of misoprostol, this cost was included in the analysis. However, for the participants who used them, additional doses of misoprostol were costed. Within the NHS, the practice is to use oral tablets for vaginal and sublingual administration; therefore, irrespective of the route the same cost was applied for all misoprostol usage.

Health utility data were collected at baseline, at 6 or 7 days and at 21 days post-randomisation and at discharge from EPU care, using the EQ-5D-5L questionnaire. For women in the trial that had a negative pregnancy test following the intervention, day 21 was the point of discharge.

Missing data

Multivariate regressions and Student's *t*-tests were used to assess whether the missing data could be predicted by other variables in the existing data.[15] If the associations between variables were not statistically significant at the 5% level, data were assumed to be missing completely at random. Missing values were imputed using multiple imputations by applying chained equations with predictive mean matching across 25 imputations.[16,17]

Model-based economic evaluation

The key costs used in the model are also presented in Table 1. Except for surgical intervention, the unit costs applied in the model are equivalent to those used in the within-trial analysis. Further details on resource use are provided in Table S2.

Analysis

The within-trial and model-based incremental cost-effectiveness analyses (ICEA) were based on the primary outcome of additional cost per additional successfully managed miscarriage. For the CUA, the interim crosswalk EQ-5D-5L value set for the UK population was applied to convert utility scores to EQ-5D-5L values.[18] Here, the EQ-5D-5L scores were mapped back to the EQ-5D-3L valuation set.[19] QALYs were estimated with the area-under-the-curve method using the trapezoidal rule, which links the utility scores of each participant at different time points. To avoid bias, multiple linear regressions with baseline EQ-5D-5L utility (plus other minimisation variables) as a covariate were used to adjust for any difference between the trial arms.[20]

Mean total cost and resource use for participants across trial arms were calculated for the within-trial analysis. Given the skewness inherent in cost and QALYs data, the bias-corrected and accelerated (BCa) nonparametric bootstrap method was applied to estimate 95% confidence intervals (95% CIs) around mean differences by analysing 1000 resamples.[21] Multivariate cost analyses were conducted using seemingly unrelated regressions to assess heterogeneity in the trial population.[22,23] Based on the minimisation variables for the trial, model covariates included baseline data on maternal age (<30 or ≥30 years), body mass index (BMI, <35 or ≥35 kg/m^2), gestational age (<70 or ≥70 days) and quantity of bleeding (pictorial blood assessment chart, PBAC, score: 0–4; 0=no bleeding, 4=heavy bleeding).

Details of the model-based analysis are presented in Appendixes S3 and S4. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in mean cost between the trial arms by the difference in the relevant outcomes.

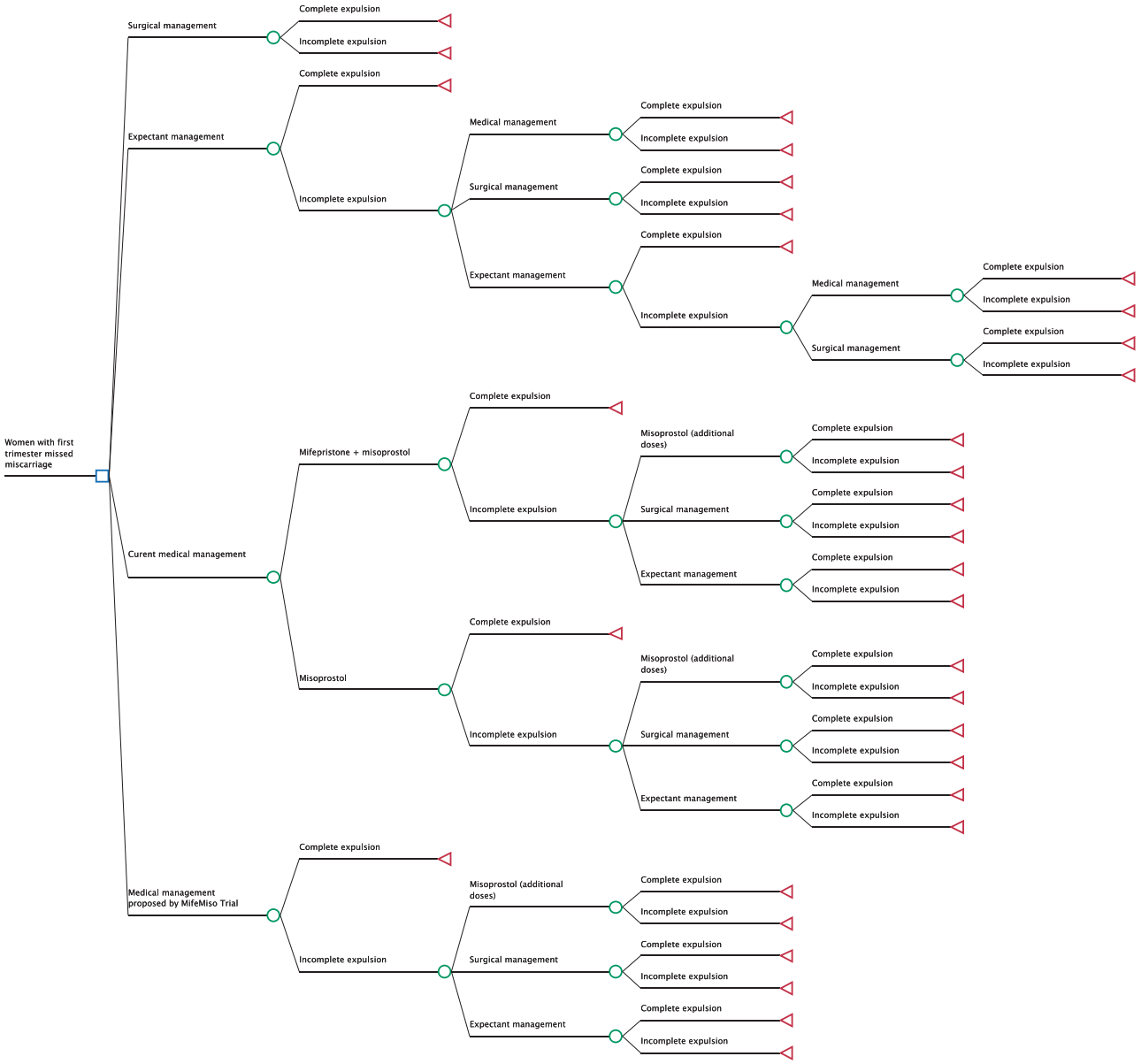

Figure 1. Model pathway.

All analyses took the perspective of the NHS as a result of prospective data collection in the trial and a reliance on secondary data for the model. The time horizon for all analyses was less than a year; therefore, discounting was not applied. Analyses were performed using TREEAGE PRO 2020 or STATA 14.[11,24] The analysis is reported following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[25]

Trial and model-based sensitivity analysis

To quantify the uncertainty often attributable to sampling variations, assumptions and perspectives, sensitivity analyses were undertaken. These included stochastic/probabilistic sensitivity analyses (PSAs) and one-way deterministic analyses (DSAs).

Stochastic and probabilistic sensitivity analyses. For the within-trial analysis, stochastic sensitivity analyses were carried out for the base case. The joint distribution in the mean cost and outcome differences between the trial arms were resampled using nonparametric bootstrapping (seemingly unrelated estimates).[26] The distributions were simulated 5000 times to generate paired estimates of incremental costs and successfully managed miscarriages, which were plotted as scatter plots in a cost-effectiveness plane.[27] Cost-effectiveness acceptability curves (CEACs)

Table 1. Unit costs of resource items (prices in £, 2019–20)

Resource use items	Unit cost (£)[a]	HRG code/other information	Source[b]
Medication/medical management[c]			
Mifepristone (Mifegyne®)	18	Per 200 mg tablet	BNF 2019
Misoprostol (Topogyne®)	16	Per 800 microgram tablet	BNF 2019
Misoprostol (Mysodelle®)[d]	372	Per 800 microgram pessary	BNF 2019
Secondary care costs			
Hospital visit	150	Scheduled visit	PSSRU 2002
Emergency visit	98	VB09Z VB11Z	NHS reference cost 2018–19
Outpatient admission (specialised nonroutine Ultrasound)	127	NZ22Z	NHS reference cost 2018–19
Inpatient admission (<24 hours)	325	MA54Z MA55A MA55B MA56A MA56B	NHS reference cost 2018–19
Night of patient admission	413	MA51Z MA52A MA52B MA54Z MA55B	NHS reference cost 2018–19
Surgical management (dilation and evacuation)	1462	MA17C MA17D	NHS reference cost 2017–18
Manual vacuum aspiration (MVA)	1182	MA19A MA19B	NHS reference cost 2017–18
Surgical management[c]			
Surgical Intervention (stage 2, medical management with mifepristone plus misoprostol)	1400	Per procedure. Weighted cost based on 78% D&E/22% MVA	NHS reference costs 2016–17
Surgical intervention (stage 1, surgical management)	1254	Per procedure, <14 weeks of gestation. Weighted cost based on assumption of 77% D&E /23% MVA[e]	NHS reference costs 2016–17
Surgical Intervention (stages 2 and 3, expectant management and current medical management)	1398	Per procedure, <14 weeks of gestation. Weighted cost based on assumption of 77% D&E /23% MVA[e]	NHS reference costs 2016–17

NHS, National Health Service; PSSRU, Personal Social Services Unit.
Serious adverse events (SAEs) costs not included as there were no SAEs clearly related to the administration of the intervention.
[a]Inflated to 2019–20 costs using the UK NHS pay and prices index.
[b]Taken from NHS reference costs (2018–19), unless otherwise stated. Where the NHS categories differ from ours, data were extracted from the closest match. Where there are different categories associated with resource use, weighted averages were used.
[c]Costs used for the model-based analysis only.
[d]Used for the sensitivity analysis.
[e]Assumption derived from the results of both groups of the MifeMiso trial.

were generated to depict the probabilities that the use of MifeMiso for the medical management of miscarriages is a cost-effective intervention compared with misoprostol alone across a range of values representing the decision maker's willingness to pay (WTP) for an additional benefit.[10] Typically, ICERs are compared against the benchmark thresholds for cost-effectiveness in the NHS context of £20,000 to £30,000 per QALY gained.[10]

For the model-based probability sensitivity analysis (PSA), each uncertain model input parameter was assigned a distribution, from which a value was randomly drawn. We computed 10 000 Monte Carlo simulations, which generated mean cost and effectiveness estimates by simultaneously varying all relevant parameters. These estimates were used jointly to form an empirical distribution of the differences in both the cost and effectiveness of interventions.

Where two outcomes were possible, beta distributions were applied to probabilities, and if three outcomes were possible, Dirichlet distributions (the multinomial extension of the beta distribution) were applied. Gamma distributions were applied to resource use and costs. When resource use data were derived from alternative strategies or only point estimates were available the widest possible uncertainty was applied.

Deterministic sensitivity analyses. A full range of deterministic sensitivity analyses was conducted on the input parameters for the base case and are presented in Appendix S5.

Results

Within-trial economic evaluation results

The results of the randomised controlled trial (RCT) for MifeMiso are reported in detail elsewhere.[7] Seven hundred and eleven women were recruited, from which 357 women

and 354 women were randomised to the mifepristone plus misoprostol arm and the placebo plus misoprostol arm, respectively. Six (0.8%) women withdrew from the trial, whereas seven women (1%) were lost to follow-up.[7]

The primary outcome was missing for two women (0.3%) and the within-trial economic analysis was based on 696 women, with 348 women in each arm. The primary outcome (Table 2) was achieved by 289 women (83%) in the intervention arm and 266 women (76%) in the placebo arm, an absolute effect difference of 6.6% (95% CI 0.7–12.5%).

The resource use data (Table S3) shows that women in the placebo arm on average used more resources than women in the intervention arm. The exception was the inpatient overnight admissions. These differences are reflected in the costs (Table 3). The mean total costs per woman for the trial period was £621 in the intervention arm and £803 in the placebo arm, generating a mean cost difference of –£182 (95% CI −£338 to −£26) (Table 3).

Cost-effectiveness analysis

The CEA results suggest that the MifeMiso intervention was more effective than misoprostol only, with a gain of seven successfully managed miscarriages per 100 women (Table 4). The intervention resulted in a cost saving of £182 (95% CI £26–£338) per successfully managed miscarriage.

The results of the stochastic CEA based on 5000 bootstrap replications are plotted on the cost-effectiveness plane for the base-case analysis and are presented in Figure 2. Each point on the plane depicts a pair of incremental cost and incremental effectiveness estimates for the comparison between the trial arms. The majority of the scatter plot dots are in the south-east quadrant. This suggests that MifeMiso intervention is dominant, i.e. less costly and more effective than the comparator of misoprostol alone.

Figure 3 presents the CEAC for the base-case analysis, which illustrates the probability of the intervention being cost-effective for various values of decision makers' WTP per additional successfully managed miscarriage. For thresholds of WTP greater than £3000, the probability of the MifeMiso intervention being cost-effective is over 90% (Figure 3).

Cost–utility analysis

Details of all findings are available in Table S4. Complete EQ-5D-5L data were available for 593 women (85%) (296 in the intervention arm and 297 in the placebo arm). Of particular note are the data collected on discharge from the EPU, for which data were available for less than 17% of the participants. The poor data available for this variable is mostly because the last contact for women that had a negative pregnancy test following the intervention was day 21.

The limited data for this variable and the variation in discharge points meant that it is inappropriate to include this in the analysis, and hence the end point for all analyses was day 21. Multiple imputations were used to calculate missing data up to day 21. The CUA results showed a QALYs difference of 0.04% (95% CI −0.01 to 0.1%) (Table 4). The MifeMiso intervention remained cost-saving.

The stochastic analysis for the CUA is presented in Figure S1A. The majority of the scatter plot dots are in the south-east quadrant, suggesting that the MifeMiso intervention is dominant, i.e. less costly and more effective than the comparator. The CEAC (Figure S1B) shows that for WTP thresholds of £3000 and above, the probability of MifeMiso being cost-effective is over 90%.

Model-based economic evaluation

The model-based analysis showed that MifeMiso intervention is the least costly strategy, with a mean cost of £761 per woman (Table 4). The most effective strategy is surgical management, whereas MifeMiso intervention is the second most effective strategy. Both the current medical management and expectant management strategies are dominated by the MifeMiso intervention, as they are more costly and

Table 2. Clinical outcomes

Outcomes	Mifepristone + misoprostol (*N* = 348)		Placebo + misoprostol (*N* = 348)		Bootstrap difference (95% CI)		
	n/N %	*N*	*n/N* %	*N*	Adjusted mean	Lower CI	Higher CI
Primary outcome							
Successfully managed miscarriage	83.1	289	76.4	266	6.6	0.6	12.5
Other clinical outcomes							
Need for surgery	17.8	62	25.0	87	7.2	13.3	1.1
Surgery complication	6.5	4	5.8	5	0.3	1.9	1.4
Need for additional misoprostol	14.4	50	18.7	65	4.3	9.7	1.1

Table 3. Disaggregated costs by trial arms (prices in £, 2019–20)

Cost Items	Mifepristone + misoprostol (*N* = 348)		Placebo + misoprostol (*N* = 348)		Bootstrap mean cost difference (95% CI)[a]		
	Mean	SD	Mean	SD	Adjusted Mean difference	Lower CI	Higher CI
Intervention	18	0	0	0			
Secondary care							
Hospital visit	100	177	138	198	−37	−65	−9
Emergency visit	18	42	28	64	−10	−18	−2
Outpatient admission (specialised non-routine Ultrasound)	50	125	64	128	−14	−33	−6
Inpatient admission (<24 hours)	68	148	92	172	−24	−48	−0.79
Night of patient admission	81	323	71	213	11	−31	53
Additional dose of misoprostol	3	8	4	9	−0.77	−2	0.5
Surgical management (dilation and evacuation)	197	500	281	577	−85	−165	−4
Manual vacuum aspiration	50	240	68	276	−17	−55	22
Mean total costs							
Hospital visits/admissions	328	629	388	556	−58	−148	32
Need for surgery	248	537	349	609	−101	−185	−18
Additional dose of misoprostol	3	8	4	9	−0.77	−2	0.5
Mean total cost	580	1012	741	1028	−161	−309	−12

[a]The difference has been adjusted to take into account the minimisation variables.

Table 4. Cost per point change in outcomes (means and 95% CIs)

Treatment	Mean cost (£)	Mean effect	Cost difference (£) (95% CI)	Effect difference (95% CI)	ICER (£)
Primary outcome					
Mifepristone + misoprostol	621	0.831	−182 (−338 to −26)	6.6 (0.7–12.5)	Dominant
Placebo + misoprostol	803	0.764			
QALYs					
Mifepristone + misoprostol	621	0.0324	−182 (−338 to −26)	0.04 (−0.01 to 0.1)	Dominant
Placebo + misoprostol	803	0.0319			
Base-case analysis for the model					
Medical management with mifepristone + misoprostol	761	0.830			
Current medical management	876	0.717			Dominated
Expectant management	1177	0.289			Dominated
Surgical management	1658	0.959			6969.13

Costs and ICERs are reported to the nearest pound.

less effective than the intervention. However, surgical management was found to be more costly and more effective than MifeMiso intervention, with an estimated ICER of £6969 per additional miscarriage successfully managed.

The PSA, which explored the uncertainty of the model inputs, showed moderate uncertainty (Figure 4A). The CEAC for MifeMiso intervention and surgical management (Figure 4B) shows that given an arbitrary WTP threshold of £5000, the probability that the MifeMiso intervention is cost-effective is 86%. However, if the WTP threshold exceeds £10,000, the probability that the MifeMiso intervention is cost-effective falls to 15%, whereas the probability that surgical management is cost-effective increases to 85%. As the WTP tends to infinity, the probability that surgical management is cost-effective compared with the MifeMiso intervention tends to 99%.

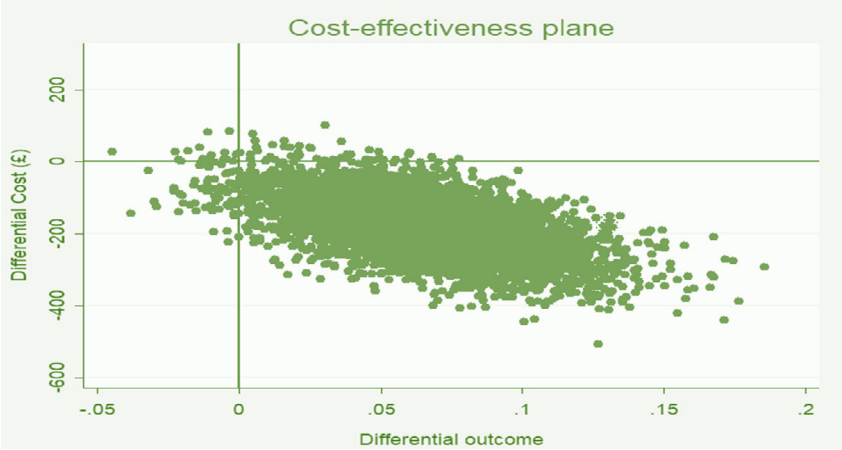

Figure 2. Cost-effectiveness plane for the primary outcome.

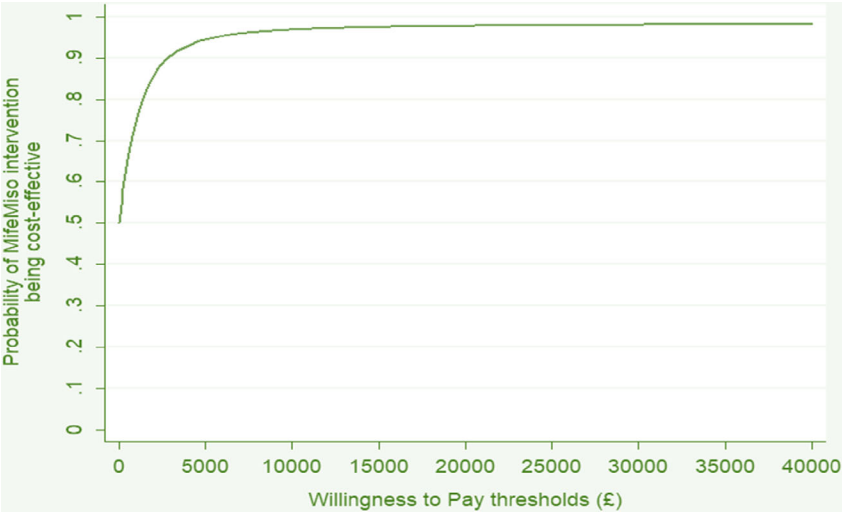

Figure 3. Cost-effectiveness acceptability curve for the primary outcome.

Deterministic sensitivity analysis

The sensitivity analyses results are provided in Table S5. For all scenarios in the trial-based and model-based analyses, the results made no substantial difference to the base-case results.

Discussion

Principal findings

The main analysis was a CEA in terms of cost per successfully managed miscarriage. A CUA in terms of cost per QALY was also conducted. The results of the primary CEA suggest that the MifeMiso trial intervention (mifepristone plus misoprostol) was less costly than the use of misoprostol only, with a cost saving of £182 (95% CI £26–£338). The trial intervention is also more effective and led to an additional 66 completely resolved miscarriages per 100 women (6.6%, 95% CI 0.7–12.5%). Hence, the mifepristone plus misoprostol is less costly and more effective, which suggests that the MifeMiso intervention is dominant compared with the use of misoprostol alone. The CUA showed that the intervention was dominant, with a cost saving of £182 (95% CI £26–£338) and a QALYs difference of 0.04% (95% CI −0.01 to 0.1%).

The model-based analysis showed that for the management of a missed miscarriage the MifeMiso intervention is dominant when compared with expectant management and the current medical management strategy. However, the intervention is less effective but less costly than surgical management, with an ICER of £6969 per additional successfully managed miscarriage. The PSA suggests that at WTP thresholds below £7000 the intervention is preferred, relative to surgical management, but that at higher WTP thresholds surgery becomes the preferred strategy on cost-effectiveness grounds.

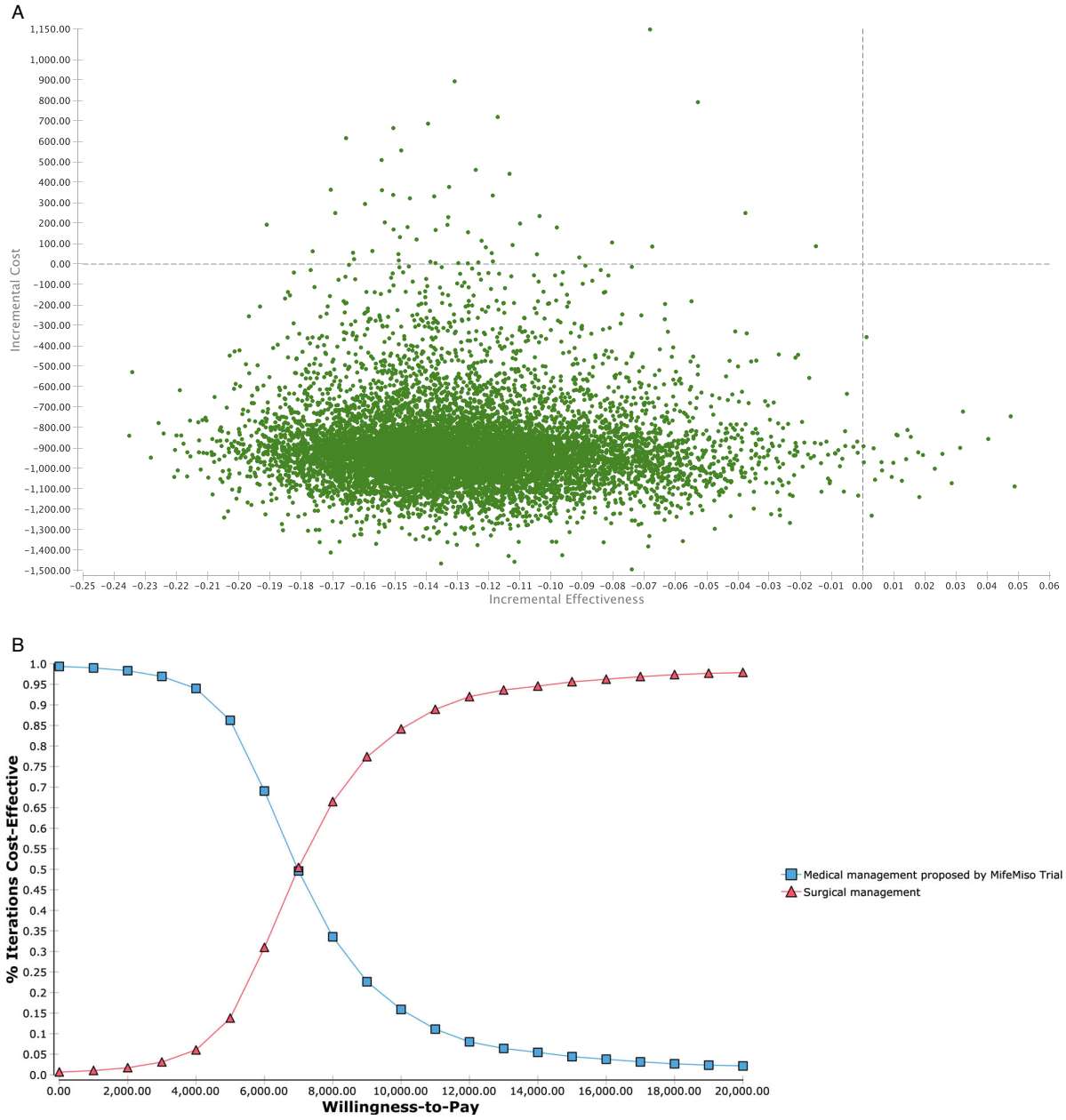

Figure 4. (A) Cost-effectiveness plane for medical management with mifepristone plus misoprostol relative to surgical management. (B) Cost-effectiveness acceptability curve for medical management with mifepristone plus misoprostol compared with surgical management.

Sensitivity analyses were conducted to explore whether the robustness of primary analysis results in changes in the assumptions. The conclusions drawn from all analyses were shown to be robust to all sensitivity analyses.

Strengths and limitations

A key strength of the trial-based analysis is that it was conducted in keeping with the recommended design and reporting guidelines. It was based on a multicentre RCT and provided the channel for prospective data collection. Data were collected during the trial using case report forms (CRFs) and at specified time points. Unit costs were drawn from established national sources, and where variables were not clearly depicted by healthcare resource groups (HRGs), we collaborated with the clinical teams to select the most suitable HRG. These are likely to enhance the

generalisability of the findings of the study. The robustness of the main analyses, as evidenced by the sensitivity analyses, is a strength.

Also, we carried out a CUA, thereby further measuring the effectiveness of the trial intervention in terms of QALYs, as recommended by NICE.[10] The use of a preference-based measure of health outcome is more useful for comparative purposes. However, some EQ-5D-5L data were missing, which we accounted for by imputing missing values. Although imputation is not ideal, the results are robust to these methods, as the complete case analysis shows similar results. Nonetheless, the CUA result may or may not be individually linked to the successful outcome or otherwise of the intervention.

A strength of the model-based analysis is that it is the first model to compare the cost-effectiveness of the three broad alternative management strategies exclusively for missed miscarriage. The model considered the cost-effectiveness of a management strategy – as proposed by a clinical trial – in the context of all available current practice. Being able to compare alternative management strategies and rank them in terms of cost and effectiveness is especially useful for policymakers.

The principal limitation of the model is that in the absence of a network meta-analysis on the management strategies for missed miscarriage over the relevant intervention period, the effectiveness data were based on the results of published clinical trials. Although the quality and relevance of the trials were stringently assessed, biases may be attached to the trials that could compromise the accuracy of the data. Furthermore, not all relevant data were available for all management strategies. This meant that assumptions had to be made from within the research study team. Attempts were made to ensure that appropriate assumptions were used for the missing data and the significance of these assumptions was tested in the sensitivity analysis, to try to rectify this limitation.

Information on the impact on quality of life (QoL) was not available for all management strategies included in this analysis; therefore, the outcome for the model was expressed in terms of clinical effectiveness rather than in terms of the standard unit of benefit, the QALY. Thus, the meaning of the results is less easy to interpret. Lastly, the model makes no comparisons for different dosages of mifepristone and misoprostol or for different routes of administration.

Comparison with the literature

To our knowledge, this is the first UK-based economic evaluation of the cost-effectiveness of mifepristone plus misoprostol versus misoprostol alone for the medical management of a missed miscarriage. A recent study in the USA assessed the relative cost-effectiveness of the two alternatives for the management of early pregnancy loss from the healthcare sector and societal perspective, and reported their results in terms of QALYs at 30 days post-intervention.[28] The study found mifepristone and misoprostol to be cost-effective for the healthcare sector and a dominant intervention for society.[28]

Furthermore, there is currently no published evidence on the cost-effectiveness of medical management with mifepristone plus misoprostol, compared with alternative management strategies that include surgical and expectant management, for the successful management of missed miscarriage.

Implications for policy

All economic analyses conducted in this study found that MifeMiso is likely to be perceived as a cost-effective intervention for the medical management of women presenting with a missed miscarriage. When alternative methods of miscarriage management are considered in the model, the results suggest that the best choice is between medical management with mifepristone plus misoprostol and surgical management, but that medical management with mifepristone plus misoprostol is likely to be recommended by decision makers ahead of expectant management and the current practice of medical management.

Conclusion

The within-trial economic evaluation found that the combination of mifepristone and misoprostol is likely to be recommended by decision makers for the medical management of women presenting with a missed miscarriage based on cost-effectiveness grounds.

The model-based analysis shows that MifeMiso intervention is dominant (more effective and less costly) when compared with expectant management and with the current medical management strategy. However, the intervention is a less effective strategy than surgical management, although it is less costly. Thus, when alternative methods of miscarriage management are considered, the results suggest that there is a clear choice between MifeMiso intervention and surgical management. However, for medical management alone, medical management with MifeMiso should be recommended by decision makers ahead of expectant management and other medical options.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

TER was responsible for the design of the economic evaluation and was co-applicant with AC, JC, AD, PH, LJ, RB-A,

JB, KH, MC, AWH and SQ. LEB was the trial manager and contributed to data collection. AA, MC, JN, CB, NN, AO, FI, KB, IH, YJ, JH, SD, JR, LW, MU, YC, CSK, SP, FH, PG, RS, AS, AWH and SQ were responsible for the oversight of the study at their respective hospitals and contributed to the recruitment of participants. VC, YS and PH were responsible for data analysis. IDG performed the updated meta-analysis. All authors contributed to data interpretation. CO was responsible for the first draft of this article, in collaboration with EW. CO carried out the trial-based analysis and EW carried out the model-based analysis. TER oversaw the economic analysis and revised the article. All authors contributed to the editing and revision of the article and gave final approval.

Details of ethics approval

Ethical approval was granted by the UK Medicines and Healthcare Products Regulatory Authority (MHRA), the UK National Research Ethics Service Committee (West Midlands—Edgbaston; REC reference: 17/WM/0017) and the National Health Service Research and Development department at each participating hospital. Initial REC approval was received on 14 February 2017 and we received HRA approval on 18 April 2017.

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Data availability statement

The data that supports the findings of this study are available in the supporting information for this article.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Inclusion and Exclusion Criteria for the MifeMiso Trial.

Appendix S2. Details of the Model Pathway Comparing the different miscarriage management strategies.

Appendix S3. Details of the Resource Use Data for the Model.

Appendix S4. Model assumptions.

Appendix S5. Deterministic sensitivity analysis for the Trial-based and Model-Based Analyses.

Figure S1. (A) Cost-effectiveness plane for the CUA (complete case analysis). (B) Cost-effectiveness acceptability curve for the CUA (complete case analysis).

Table S1. (A) Effectiveness data for alternative management strategies. (B) Data on the probability of undergoing management strategies. (C) Probabilities from the MifeMiso trial.

Table S2. (A) Resource use data for the model branches populated by secondary sources. (B) Resource use data for the model branch based on the MifeMiso trial.

Table S3. Mean resource use by trial arm.

Table S4. (A) EQ-5D response rates. (B) Utility and QALY estimates: EQ-5D-5L scores.

Table S5. (A) Sensitivity analysis for the CEA. (B) Sensitivity analyses for the CUA. (C) Deterministic sensitivity analyses for the model. ■

References

1 Wilson R, Jenkins C, Miller H, McInnes IB, Moore J, McLean MA, et al. Abnormal cytokine levels in non-pregnant women with a history of recurrent miscarriage. *Eur J Obstet Gynecol Reprod Biol* 2004;115:51–4.

2 Jurkovic D, Overton C, Bender-Atik R. Diagnosis and management of first trimester miscarriage. *BMJ* 2013;346:f3676.

3 Regan L, Rai R. Epidemiology and the medical causes of miscarriage. *Best Pract Res Clin Obstet Gynaecol* 2000;14:839–54.

4 Kong G, Chung T, Lai B, Lok I. Gender comparison of psychological reaction after miscarriage—a 1-year longitudinal study. *BJOG* 2010;117:1211–9.

5 Newbatt E, Beckles Z, Ullman R, Lumsden MA. Ectopic pregnancy and miscarriage: summary of NICE guidance. *BMJ* 2012;345:e8136.

6 Chu J, Hardy P, Beeson L, Coomarasamy A. What is the best method for managing early miscarriage? *BMJ* 2020;368:l6438.

7 Chu JJ, Devall AJ, Beeson LE, Hardy P, Cheed V, Sun Y, et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. *Lancet* 2020;396:770–8.

8 National Collaborating Centre for Women's and Children's Health. *Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage*. London: National Collaborating Centre for Women's and Children's Health; 2012.

9 Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertil Steril* 2006;86:956–60.

10 NICE. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence; 2013.

11 TreeAge Pro. 2020. R1. TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.

12 Gallos ID, Williams HM, Price MJ, Eapen A, Eyo MM, Tobias A, et al. Methods for managing miscarriage: a network meta-analysis. *Cochrane Database Syst Revi* 2017;2017:CD012602.

13 National Schedule of Reference Costs, 2018-19 –NHS trusts and NHS foundation trusts [Internet]. 2019. [https://www.england.nhs.uk/national-cost-collection/#ncc1819]. Accessed 20 February 2020.

14 Curtis LA, Burns A. *Unit Costs of Health and Social Care 2019*. Kent: PSSRU; 2019.

15 Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.

16 Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 2004.

17 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.

18 van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15:708–15.

19 Position statement on use of the EQ-5D-5L value set for England. 2017 [www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l]. Accessed 26 March 2020.

20 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96.

21 Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000;19:3219–36.

22 Zellner A, Huang DS. Further properties of efficient estimators for seemingly unrelated regression equations. *Int Econ Rev* 1962;3:300–13.

23 Moon H, Perron B. Seemingly unrelated regressions. In: Durlauf SN, Blume LE, editors. *The New Palgrave Dictionary of Economics*. London: Palgrave Macmillan; 2008.

24 Stata Corp LP. *Stata Statistical Software Release 15*. College Station: Stata Press Publication; 2017.

25 Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231–50.

26 Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. *Expert Rev Pharmacoecon Outcomes Res* 2001;1:25–36.

27 Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making* 1990;10:212–4.

28 Nagendra D, Koelper N, Loza-Avalos SE, Sonalkar S, Chen M, Atrio J, et al. Cost-effectiveness of mifepristone pretreatment for the medical management of nonviable early pregnancy: secondary analysis of a randomized clinical trial. *JAMA Network Open* 2020;3:e201594.