Research questions

Question number	**1**				**Notes**
Date of consideration	5 October 2017				
New Question (in full)	**In Rh D negative pregnant women with no preformed anti-D, does *universal*[1] routine antenatal prophylaxis with Rh D immunoglobulin (1 or 2 doses) prevent Rh D alloimmunisation?**				
Subquestions (in full)	**In Rh D negative pregnant women with no preformed anti-D, is *universal* routine antenatal prophylaxis with one dose of Rh D immunoglobulin as effective at preventing Rh D alloimmunisation as *universal* routine prophylaxis with two doses of Rh D immunoglobulin?**				The evidence for this question will come from the same evidence base as identified for the above question – so it is included as a subquestion rather than a separate question
Question type	Population	Intervention	Comparator	Outcome	*Importance of outcome*[2]
Main Question (Intervention)	Rh D negative pregnant women with no preformed anti-D	Routine antenatal prophylactic Rh D immunoglobulin Stratify by: • 1 or 2 doses • 1 dose only • 2 doses only	Placebo or no routine antenatal prophylactic Rh D immunoglobulin	• incidence of Rh D alloimmunisation[3] • incidence of a positive test for feto-maternal haemorrhage[4] (e.g. Kleihauer test, flow cytometry) • adverse neonatal events (e.g. jaundice) • adverse maternal events attributed to anti-D (e.g. allergic response, infection)	Critical Not Important If available[5] If available[e]
Subquestion *(Intervention)*	Rh D negative pregnant women with no preformed	1-dose routine antenatal prophylactic Rh D	2-dose routine antenatal prophylactic Rh D	• incidence of Rh D alloimmunisation • adverse neonatal events (e.g.	Critical If available[e]

[1] Includes all pregnant women who are Rh D negative with no preformed anti-D.

[2] Critical, important or resource use.

[3] Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present).

[4] The ERG debated whether to include 'incidence of a positive Kleihauer test' as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important.

[5] Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted.

Question number	**1**				**Notes**
	anti-D	immunoglobulin	immunoglobulin	jaundice) • adverse maternal events (e.g. allergic response, infection)	If available[e]
Additional information					
Data to extract	Number of pregnancies	Product type Mode of administration Number of doses Dosage Timing	<u>Subquestion only</u> Product type Mode of administration Dosage Timing	<u>Rh D alloimmunisation</u> Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy) <u>Kleihauer test / flow cytometry</u> At potentially sensitising events and postpartum [after birth of a Rh-positive infant]) <u>Adverse neonatal events</u> Timing (current or subsequent pregnancy) and severity <u>Adverse maternal events</u> Timing and severity	

Source: Anti-D scoping report (Health Research Consulting, November 2017)

Question number	**2**				**Notes**
Date of consideration	05 October 2017				
New Question (in full)	**In Rh D negative women with no preformed anti-D who have experienced one of the following first trimester[6] sensitising events – abdominal trauma, molar pregnancy, ectopic pregnancy, spontaneous miscarriage, threatened miscarriage or medical termination of pregnancy (with/without a curette), does *universal*[7] first-trimester sensitising event prophylaxis with Rh D immunoglobulin prevent Rh D alloimmunisation?**				
Subquestions (in full)	--				
Question type	*Population*	*Intervention*	*Comparator*	*Outcome*	*Importance of outcome*[8]
Main Question *(intervention)*	Rh D negative women with no preformed anti-D with a first-trimester sensitising event, specifically: • abdominal trauma • molar pregnancy • ectopic pregnancy • spontaneous miscarriage • threatened miscarriage • medical termination of pregnancy (with/without a curette)	First trimester sensitising event prophylactic Rh D immunoglobulin	Placebo or no first trimester sensitising event prophylactic Rh D immunoglobulin	• incidence of Rh D alloimmunisation[9] • incidence of a positive test for feto-maternal haemorrhage[10] (e.g. (Kleihauer test, flow cytometry) • adverse neonatal events (e.g. jaundice) • adverse maternal events attributed to anti-D (e.g. allergic response, infection)	Critical Not important If available[11] If available[k]
Additional information					
Data to extract	Number of pregnancies Timing of sensitising event Nature of sensitising event	Product type Mode of administration Number of doses		<u>Rh D alloimmunisation</u> Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and	

[6] The definition of first trimester varies across countries and for this review will be defined by the literature. The definition used by each included study should be extracted.

[7] Includes all pregnant women who are Rh D negative with no preformed anti-D.

[8] Critical, important or resource use.

[9] Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present).

[10] The ERG debated whether to include 'incidence of a positive Kleihauer test' as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important.

[11] Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted.

Question number	2				Notes
	Use of curette	Dosage Timing		subsequent pregnancy) <u>Kleihauer test / flow cytometry</u> At potentially sensitising events and postpartum [after birth of a Rh-positive infant]) <u>Adverse neonatal events</u> Timing (current or subsequent pregnancy) and severity <u>Adverse maternal events</u> Timing and severity	

Source: Anti-D scoping report (Health Research Consulting, November 2017)

Question number	**3**				**Notes**
Date of consideration	05 October 2017				
New Question (in full)	**In Rh D negative pregnant women with no preformed anti-D, does *targeted*[12] routine antenatal or sensitising event prophylaxis to women with a Rh D positive fetus increase the incidence of Rh D alloimmunisation compared with *universal*[13] routine antenatal or sensitising event prophylaxis?**				
Subquestions (in full)	**In Rh D negative pregnant women with no preformed anti-D, what is the diagnostic accuracy of noninvasive prenatal screening to identify fetal Rh D status?**				
Question type	*Population*	*Intervention/Test*	*Comparator and/or reference standard*	*Outcome*	*Importance of outcome*[14]
Main Question *(Screening)*	Rh D negative pregnant women with no preformed anti-D	*Targeted* administration of prophylactic Rh D immunoglobulin (based on noninvasive prenatal screening) Stratify by: • any prophylaxis • routine antenatal prophylaxis • sensitising event antenatal prophylaxis	*Universal* administration of prophylactic Rh D immunoglobulin Stratify by: • any prophylaxis • routine antenatal prophylaxis • sensitising event antenatal prophylaxis	• incidence of Rh D alloimmunisation[15] • utilisation of anti-D • incidence of a positive test for feto-maternal haemorrhage[16] (e.g. Kleihauer test, flow cytometry) • adverse neonatal events (e.g. jaundice) • adverse maternal events attributed to anti-D (e.g. allergic response, infection)	Critical Resource use Not important If available[17] If available[f]
Subquestion *(Diagnostic)*	Rh D negative pregnant women with no preformed anti-D	Noninvasive prenatal testing for fetal Rh D status	Postnatal cord blood testing (or other neonatal sample) for fetal Rh D status Other noninvasive fetal RhD determination	• sensitivity • specificity • false positives • false negatives • positive likelihood ratio	Critical Critical Critical Critical Important Important

[12] Includes pregnant women who are Rh D negative with no preformed anti-D with a Rh D positive fetus identified via first trimester non-invasive prenatal screening.

[13] Includes all pregnant women who are Rh D negative with no preformed anti-D.

[14] Critical, important or resource use.

[15] Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present).

[16] The ERG debated whether to include 'incidence of a positive Kleihauer test' as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important.

[17] Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted.

Question number	**3**				**Notes**
				• negative likelihood ratio	
Additional information					
Data to extract	Number of pregnancies BMI	<u>Screening question</u> Product type Number of doses Dosage Timing Testing methodology Timing <u>Diagnostic question</u> Testing methodology Timing	<u>Screening question</u> Product type Number of doses Dosage Timing <u>Diagnostic question</u> Testing methodology Timing	<u>Rh D alloimmunisation</u> Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy) <u>Utilisation</u> Rates <u>Kleihauer test /flow cytometry</u> At potentially sensitising events and postpartum [after birth of a Rh-positive infant]) <u>Adverse neonatal events</u> Timing (current or subsequent pregnancy) and severity <u>Adverse maternal events</u> Timing and severity <u>Diagnostic accuracy</u> Timing of test	

Source: Anti-D scoping report (Health Research Consulting, November 2017)

Question number	**4**			**Notes**
Date of consideration	05 October 2017			
New Question (in full)	**In Rh D negative pregnant or postpartum women with no preformed anti-D, does increasing BMI increase the risk of failure of anti-D administration?**			
Subquestions (in full)	--			
Question type	*Population*	*Prognostic/Risk factor*	*Outcome*	*Importance of outcome*[18]
Main Question *(prognostic)*	Rh D negative pregnant or postpartum women with no preformed anti-D receiving prophylactic Rh D immunoglobulin Stratify by • pregnant women • postpartum women	• BMI (dichotomous or continuous) • weight • any other weight-related factors examined	• incidence of Rh D alloimmunisation[19] • anti-D levels [20] • incidence of a positive test for feto-maternal haemorrhage (e.g. (Kleihauer test, flow cytometry)[21] • adverse neonatal events (e.g. jaundice) • adverse maternal events (e.g. allergic response, infection)	Critical Critical (if data for Rh D alloimmunisation is not available) Not important If available If available (particularly if increased dose or different mode of administration/technique used)
Additional information				
Data to extract	Product type Mode of administration Number of doses/dosage Timing of administration Administration technique	Specific details of weight-related risk factors	<u>Rh D alloimmunisation</u> Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant] up to 12 months and subsequent pregnancy) <u>Anti-D levels</u> Timing <u>Kleihauer test /flow cytometry</u> At potentially sensitising events and postpartum [after birth of a Rh-positive	

[18] Critical, important or resource use.

[19] Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present).

[20] This is a surrogate outcome. Measured as a continuous outcome (actual anti-D level in maternal blood). If this is used instead of Rh D alloimmunisation will need background research to look for evidence of link between lower anti-D levels and alloimmunisation.

[21] The ERG debated whether to include 'incidence of a positive Kleihauer test' as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important.

Question number	4			Notes
			infant]) <u>Adverse neonatal events</u> Timing (current or subsequent pregnancy) and severity <u>Adverse maternal events</u> Timing and severity	

Source: Anti-D scoping report (Health Research Consulting, November 2017)