Question 4. Monitoring treatment response

Table 1: Positive and negative predictive value of three best performing criteria identified in the review by Rio 2016

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Rio 2016	New T2 ≥1	EDSS worsening	4 to 4.8 years	K=2	48%	93.8%
Rio 2016	New T2 ≥2	EDSS worsening	4 to 4.8 years	K=2	55%	87.3%
Rio 2016	ModRio score ≥2	EDSS worsening	4 years	K=2	50%	75.5%

Table 2: Positive and negative predictive value of criteria located in primary studies from the updated search

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Hyun 2015	Rio Score ≥2	EDSS worsening	3 years	K=1	92%	93%
Hyun 2015	ModRio score ≥2	EDSS worsening	3 years	K=1	86%	93%
Sormani 2016	MAGNIMS ≥1	Treatment failure	3 years	K=1	34%	83%
Sormani 2016	MAGNIMS ≥1	EDSS worsening	3 years	K=1	26%	86%

Table 3: Positive and negative predictive value of NEDA from Rottstein 2015

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Rottstein 2015	NEDA	Absence of disability worsening	7 years	K=1	71.7%	40.7%-43.1%

Question 10. Treatment in special situations: pregnancy

Table 4. Impact of exposure to DMTs on pregnancy outcomes

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	**Spontaneous abortion**	**Malformations°**	**Neonatal death**	
Amato 2010	IFNb	*Exposed*	OR=1.14, 95% CI 0.41 to 3.15, p=0.803)	8% (7/88)	NR	NR	Up to 2 years
		Unexposed		6.3% (20/318)			
Boscovic 2005	IFNb	*Exposed*	NR	39% (9/23)	9% (2/23)	4% (1/23)	Not reported
		Unexposed		19% (4/21)	5% (1/21)	0%	
Coyle 2014	IFNb	*Exposed*	5.1% (3/59)[a]	11.5% (11/96)	5.8% (5/96)	NR	17 weeks post-partum
Romero 2015	IFNb	*Exposed*	0.2% (1/423)[b]	14.4% (61/423)	1.9% (8/423)	NR	Not reported
Thiel 2016	IFNb	*Exposed*	OR 0.77 (0.26-2.22 95%CI)[b]	9.6% (24/251)	3.1% (7/251)	NR	52 weeks postpartum
		Unexposed		6.7% (13/194)	5.5% (10/194)		
Herbstritt 2016	GA	*Exposed*	NR	8.6% (13/151)	2.2% (3/151)	NR	26 weeks postpartum
		Unexposed		6.3% (6/95)	6.7% (6/95)		
Giannini 2012	IFNb and GA	*Exposed (IFN)*	NR	8% (7/87)	NR	NR	Not reported
		Exposed (GA)		6% (1/17)			
		Unexposed		6% (20/311)			

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations▼	Neonatal death	
Weber-Schoendorfer & Schaefer 2009	IFNb and GA	*Exposed (GA)*	NR	4% (1/26)	8% (2/26)	NR	8 weeks post-partum
		Exposed (IFN)		12% (7/60)	6% (2/54)		
		Unexposed		10% (6/61)	9% (5/57)		
Ebrahimi 2015	NTZ IFNb and GA	*Exposed (NTZ)*	7.8% (6/77)	17.3% (17/98)	3.9% (3/77)	NR	6 months post-partum
		Exposed (IFN or GA)	7.4% (5/68)	21.1% (20/95)	1.4% (1/69)		
Hellwig 2011	NTZ	*Exposed*	NR	14.3% (5/35)	2.9% (1/35)	NR	6 months post-partum
		Unexposed		4.3% (1/23)	4.3% (1/23)		
Hellwig 2012	IFNb and GA	*Exposed (IFN)*	NR	NR	3.8% (3/78)	NR	NR
		Exposed (IGA)			4.9% (2/41)		
		Unexposed			3.2% (7/216)		
De La Heras 2007	iDMTs	*Exposed*	NR	17.6% (6/34)	No abnormalities or obstetric complications were recorded	NR	At least 3 months
		Unexposed		20.4% (11/54)			
Fernandez Liguori 2009	IFNb and GA	*Exposed*	5.8%[b]	15.6% (22/141)	4.8% (1.6-10.9%)	NR	NR
Lu 2012	IFNb and	*Exposed*	NR	NR	0% (0/21)	NR	NR

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations◤	Neonatal death	
	GA	*Previously treated*			8.8% (7/80)		
		DMD naive			5.4% (17/317)		
Fragoso 2013	IFNb and GA	*Exposed (IFN)*	0% (0/17)	0% (0/17)	0% (0/17)	0% (0/17)	46.5 months
		Exposed (GA)	4.9% (2/41)	4.9% (2/41)	2.4% (1/41)	2.4% (1/41)	
		Unexposed	2.2% (2/89)	2.2% (2/89)	0% (0/89)	0% (0/89)	
Gold 2015	DMF	*Exposed (DMF)*	NR	7.7% (3/39)	NR	NR	NR
		Placebo		15.4% (2/12)			
Karlsson 2014	FTY	Exposed△	NR	24% (12%–41%), (9/37)	5% (0.7%-18%), (2/37)§	NR	NR
Kieseier & Benamor 2014	Teriflunomide	Exposed	NR	18.8% (13/39)	No malformations noted out of 27 live births	NR	NR
Patti 2008	IFNb	*Exposed*	No significant difference between groups in birth weight	0% (0/14)	NR	NR	Until 18 months post-partum
		Previously treated		0% (0/7)			
		DMD naive		5.9% (1/17)			

¥Drug received by pregnant women in the exposed group.
†Outcomes are presented as reported in the published article; no additional analyses carried out. ‡Length of follow-up after pregnancy
◤Definitions: *Boscovic 2005* – major malformations (not defined); *Coyle 2014* – congenital malformations; *Romero 2015* – major and minor birth defects; *Thiel 2016 & Herbstritt 2016* - specified as a defect in organogenesis, major malformations as structural defects of the body and/or organs that impair viability and/or require intervention. Minor malformation was defined as small structural developmental disturbances that do not impair viability and do not need to be treated; *Weber-Schoendorfer & Schaefer 2009* – any birth defect: defined as structural abnormalities of medical, surgical, or cosmetic relevance - classified according to Merks et al. and Rasmussen, et al. Genetic syndromes were excluded; *Hellwig 2011* - NTZ: one boy with hexadactyly was born (minor malformation), Control: One girl suffered from trisomia 21 with ventricular septum defect; *Fragoso 2013* – bone malformation (not defined); *Karlsson 2014* - unilateral bowing of tibia and acrania
◊ Low birth weight was defined as <2,500g, unless specified according to the following: **(a)** Infant size was classified as 'small', 'appropriate' or 'large' for gestational age

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations▼	Neonatal death	

based on HCP assessment, **(b)** small for gestational age

Δ No valid comparator. Out of 11 participants who had received placebo during the clinical trial, 9 were elective abortions leaving 2 pregnancies as the control group.

§ Out of 24 elective abortions, n=4 were due to complications: tetralogy of Fallot (n=1); ectopic/tubal pregnancy (n=1); intrauterine death (n=1); pregnancy not developing per standard n=1