QUESTION

Should neuromodulation (i.e. stimulation, tDCS, TMS) vs. none be used for all individuals as indicated with Friedreich ataxia?	
POPULATION:	all individuals as indicated with Friedreich ataxia
INTERVENTION:	neuromodulation (i.e. stimulation, tDCS, TMS)
COMPARISON:	none
MAIN OUTCOMES:	Daily activities; Quality of life; Quality of life; Quality of life; Neurological function; Neurological function; Neurological function;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of upper limb dysfunction. 8/8 indicated the problem was serious. 1/7 indicated the problem was not urgent; 1/7 indicated probably not urgent; 1/7 indicated probably urgent; 4/7 indicated urgent. 1/7 indicated upper limb dysfunction was probably not a priority, 3/7 indicated probably a priority, 3/7 indicated priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small	An unpublished open label pilot study (n=11) in FRDA (Rowland et al) indicated that clinician led electrical stimulation and functional electrical stimulation may improve upper limb function and	

○ Moderate
● Large
○ Varies
○ Don't know

performance in daily activities in those individuals with more advanced disease and those experiencing upper limb functional limitations and did not have an impact on quality of life.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with none	Risk difference with neuromodulation (i.e. stimulation, tDCS, TMS)
Daily activities - not measured	-	-	-	-	-
Quality of life assessed with: SF36 Italian version follow up: mean 3 months	40 (1 RCT)[1]	⊕◯◯◯ VERY LOW[a,b,c,d,e]	-	20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p=0.043). The baseline SF-36 score was 54.7 (17.5) [mean(SD)] with the immediate post active tDCS 66.5 (17.5).	
Quality of life assessed with: Stroke and Aphasia Quality of Life Scale-39 Italian Version follow up: mean 3 months	20 (1 RCT)[2]	⊕◯◯◯ VERY LOW[a,b,d]	-	20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified no significant interaction in the SAQOL-39 scale (p=0.39). Mean score at baseline was 3.3 (SD 0.9), mean score immediately post sham stimulation or anodal tDCS was 3.7 (SD 0.8).	
Quality of life assessed with: World Health Organization Quality of Life	48 (1 RCT)[3]	⊕◯◯◯ VERY LOW[b,f,g]	-	Twenty-four participants underwent both intervention and sham cerebellar transcranial magnetic stimulation (cTMS) for 5 consecutive days each (28 day wash-out period in between). A Wilcoxon	

Scale				signed-rank test found no signifcant change in the WHOQOL score between the sham and intervention.
Neurological function assessed with: Scale for the Assessment and Rating of Ataxia follow up: mean 3 months	98 (4 RCTs)[1,2,3,4]	⊕◯◯◯ VERY LOW[c,d,e,h,i,j,k]	-	24 participants underwent both active and sham cTMS for 5 consecutive days each (cross-over design with 28 day wash-out period in between). A Wilcoxon signed-rank test found signifcant change (p<0.002) in the SARA score between the sham and intervention, with a within group SARA improvement of 3.3 points between baseline and post-treatment in the active group (Franca et al 2020). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a signifcant interaction in the SARA (p<0.01) (Benussi et al 2017). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p<0.001). The baseline SARA score was 20.2 (7.3) [mean(SD)] with the immediate post active tDCS 15.8 (7.6) (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed eitologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (p<0.001). The baseline SARA score was 16.3 (7.7) with the post active tDCS score 14.5 (7.8) (Benussi et al 2015).
Neurological function	98	⊕◯◯◯ VERY	-	20 participants with neurodegenerative cerebellar ataxia of mixed etiologies were

assessed with: 9HPT follow up: mean 3 months	(3 RCTs)[1,2,4]	LOW[c,d,e,h,j]		randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a signifcant interaction in the 9HPT of the non-dominant hand (*p*=0.05) and no signficant interaction in the dominant hand (Benussi et al 2016). 20 participants with neurodegenerative cerebellar ataxia of mixed etiologies were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (*p*<0.001) in the dominant 9HPT and nondominant 9HPT (*p*=0.014). The baseline dominant 9HPT hand time decreased from 53.0 (24.3) to 46.2 (21.3) sec immediately after the active tDCS (*p*<0.050). The nondominant 9HPT decreased from 56.1 (21.5) to 50.2 (20.0) post active tDCS (*p*<0.050) . (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed etiologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (*p*<0.001) in the 9HPT. At baseline, prior to the active tDCS the 9HPT time was 43.7 (17.9), post active tDCS the 9HPT time was 40.0 (17.3) sec (Benussi et al 2015).
Neurological function assessed with: ICARS follow up: mean 3 months	98 (4 RCTs)[1,2,3,4]	⊕◯◯◯ VERY LOW[c,d,h,i,j,l,m]	-	24 participants underwent both active and sham cTMS for 5 consecutive days each (cross-over design with 28 day wash-out period in between). A Wilcoxon signed-rank test found signifcant change (3.8 points, *p*=0.005) in the ICARS score between the sham and intervention, with a within group ICARS improvement of 6.1

				points (*p*=0.001) between baseline and post-treatment in the active group (Franca et al 2020). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a significant interaction in the ICARS (p<0.01). Mean ICARS score at baseline was 44.2 (SD 13.7), mean score after treatment was 35.2 (SD 15.8). (Benussi et al 2017). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p<0.001). The baseline mean ICARS score was 53.0 (SD 18.6) with the immediate post active tDCS mean score 43.0 (SD 19.6) (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed eitologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (p<0.001). The mean baseline ICARS score was 44.9 (SD 16.7) with the post active tDCS score 39.4 (17.3) (Benussi et al 2015).

1. Benussi A, Dell'Era V,Cantoni V,Bonetta E,Grasso R,et al.. Cerebello-spinal tDCS in ataxia. A randomized, double-blind, sham-controlled, crossover trial.. Neurology; 2018.
2. Benussi A, Dell'Era,Cotelli MS,Turla M,Casali C,Padovani A,Borroni B. Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia. Brain Stimulation; 2017.

	3. Franca C., de Andrade D.C.,Silva V.,et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. . Parkinsonism Relat. Disord.; 2020. 4. Benussi A, Koch G,Cotelli M,Padovani A and Borroni B. Cerebellar Transcranial Direct Current Stimulation in Patients With Ataxia: A Double-Blind, Randomized, Sham-Controlled Study. Movement Disorders; 2015. a. N=1 with diagnosis of Friedreich ataxia. b. Single study published. c. Confidence intervals not reported. d. Allocation concealment not reported or allocation not concealed from enrolling investigator. e. Potential for carryover effects in crossover trial/s. f. Participants had diagnosis of SCA3, MSA-cerebellar type & post-lesion ataxia. g. No confidence intervals reported with low absolute numbers of participants. h. In patient cohorts only n=3 had a diagnosis of Friedreich ataxia. i. Clinical scales measuring multiple domains of neurological impairment. j. Small sample sizes (n<30 per study). k. Meta-analysis not performed. Positive trends in all studies but CIs not published. l. The duration and type of neuromodulation varied between studies. Two studies had intervention period of 5 days per week for 2 weeks and one study examined a single session. Two studies examined anodal cerebellar tDCS and one study examined combined anodal cerebellar tDCS and cathodal spinal tDCS. m. Potential for carryover effects in crossover trial in two studies (Benussi et al 2015 & Benussi et al 2018).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with none	Risk difference with neuromodulation (i.e. stimulation, tDCS, TMS)
Daily activities - not measured	-	-	-	-	-
Quality of life assessed with: SF36 Italian version follow up: mean 3 months	40 (1 RCT)[1]	⊕◯◯◯ VERY LOW[a,b,c,d,e]	-	20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p=0.043). The baseline SF-36 score was 54.7 (17.5) [mean(SD)] with the immediate post active tDCS 66.5 (17.5).	
Quality of life assessed with: Stroke and Aphasia Quality of Life Scale-39 Italian Version follow up: mean 3 months	20 (1 RCT)[2]	⊕◯◯◯ VERY LOW[a,b,d]	-	20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified no significant interaction in the SAQOL-39 scale (p=0.39). Mean score at baseline was 3.3 (SD 0.9), mean score immediately post sham stimulation or anodal tDCS was 3.7 (SD 0.8).	
Quality of life assessed with:	48	⊕◯◯◯	-	Twenty-four participants underwent both intervention and sham cerebellar	

World Health Organization Quality of Life Scale	(1 RCT)[3]	VERY LOW[b,f,g]		transcranial magnetic stimulation (cTMS) for 5 consecutive days each (28 day wash-out period in between). A Wilcoxon signed-rank test found no signifcant change in the WHOQOL score between the sham and intervention.
Neurological function assessed with: Scale for the Assessment and Rating of Ataxia follow up: mean 3 months	98 (4 RCTs)[1,2,3,4]	⊕◯◯◯ VERY LOW[c,d,e,h,i,j,k]	-	24 participants underwent both active and sham cTMS for 5 consecutive days each (cross-over design with 28 day wash-out period in between). A Wilcoxon signed-rank test found signifcant change (p<0.002) in the SARA score between the sham and intervention, with a within group SARA improvement of 3.3 points between baseline and post-treatment in the active group (Franca et al 2020). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a signifcant interaction in the SARA (p<0.01) (Benussi et al 2017). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p<0.001). The baseline SARA score was 20.2 (7.3) [mean(SD)] with the immediate post active tDCS 15.8 (7.6) (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed eitologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (p<0.001). The baseline SARA score was 16.3 (7.7) with the post active tDCS score 14.5 (7.8) (Benussi et al 2015).

Neurological function assessed with: 9HPT follow up: mean 3 months	98 (3 RCTs)[1,2,4]	⊕◯◯◯ VERY LOW[c,d,e,h,j]	-	20 participants with neurodegenerative cerebellar ataxia of mixed etiologies were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a signifcant interaction in the 9HPT of the non-dominant hand (*p*=0.05) and no signficant interaction in the dominant hand (Benussi et al 2016). 20 participants with neurodegenerative cerebellar ataxia of mixed etiologies were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (*p*<0.001) in the dominant 9HPT and nondominant 9HPT (*p*=0.014). The baseline dominant 9HPT hand time decreased from 53.0 (24.3) to 46.2 (21.3) sec immediately after the active tDCS (*p*<0.050). The nondominant 9HPT decreased from 56.1 (21.5) to 50.2 (20.0) post active tDCS (*p*<0.050) . (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed etiologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (*p*<0.001) in the 9HPT. At baseline, prior to the active tDCS the 9HPT time was 43.7 (17.9), post active tDCS the 9HPT time was 40.0 (17.3) sec (Benussi et al 2015).
Neurological function assessed with: ICARS follow up: mean 3	98 (4 RCTs)[1,2,3,4]	⊕◯◯◯ VERY LOW[c,d,h,i,j,l,m]	-	24 participants underwent both active and sham cTMS for 5 consecutive days each (cross-over design with 28 day wash-out period in between). A Wilcoxon signed-rank test found signifcant change (3.8 points, *p*=0.005) in the ICARS score

months				between the sham and intervention, with a within group ICARS improvement of 6.1 points (*p*=0.001) between baseline and post-treatment in the active group (Franca et al 2020). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised anodal tDCS (n=12) and sham stimulation (n=8) for 5 days per week for 2 weeks each. A two-way mixed ANOVA (time x intervention) identified a significant interaction in the ICARS (p<0.01). Mean ICARS score at baseline was 44.2 (SD 13.7), mean score after treatment was 35.2 (SD 15.8). (Benussi et al 2017). 20 participants with neurodegenerative cerebellar ataxia of mixed diagnoses were randomised to receive anodal cerebellar tDCS and cathodal spinal tDCS or sham stimulation 5 d/wk for 2 weeks (cross-over design with 3 month wash-out period in between). An ANCOVA (time x intervention, with order of sham/active tDCS as covariate) identified a signficant interaction effect (p<0.001). The baseline mean ICARS score was 53.0 (SD 18.6) with the immediate post active tDCS mean score 43.0 (SD 19.6) (Benussi et al 2018). 19 participants with neurodegenerative ataxia with mixed eitologies were randomised to receive both anodal cerebellar tDCS and sham tDCS (crossover design with at >1wk washout) for 1 session each. A two-way repeated measures ANOVA identified a significant interaction between treament and time (p<0.001). The mean baseline ICARS score was 44.9 (SD 16.7) with the post active tDCS score 39.4 (17.3) (Benussi et al 2015).

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	current stimulation in patients with neurodegenerative ataxia. Brain Stimulation; 2017. 3. Franca C., de Andrade D.C.,Silva V.,et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. . Parkinsonism Relat. Disord.; 2020. 4. Benussi A, Koch G,Cotelli M,Padovani A and Borroni B. Cerebellar Transcranial Direct Current Stimulation in Patients With Ataxia: A Double-Blind, Randomized, Sham-Controlled Study. Movement Disorders; 2015. a. N=1 with diagnosis of Friedreich ataxia. b. Single study published. c. Confidence intervals not reported. d. Allocation concealment not reported or allocation not concealed from enrolling investigator. e. Potential for carryover effects in crossover trial/s. f. Participants had diagnosis of SCA3, MSA-cerebellar type & post-lesion ataxia. g. No confidence intervals reported with low absolute numbers of participants. h. In patient cohorts only n=3 had a diagnosis of Friedreich ataxia. i. Clinical scales measuring multiple domains of neurological impairment. j. Small sample sizes (n<30 per study). k. Meta-analysis not performed. Positive trends in all studies but CIs not published. l. The duration and type of neuromodulation varied between studies. Two studies had intervention period of 5 days per week for 2 weeks and one study examined a single session. Two studies examined anodal cerebellar tDCS and one study examined combined anodal cerebellar tDCS and cathodal spinal tDCS. m. Potential for carryover effects in crossover trial in two studies (Benussi et al 2015 & Benussi et al 2018).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low certainty of evidence as per the evidence profile table.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Daily activities - not measured	IMPORTANT[a]	-
Quality of life assessed with: SF36 Italian version follow up: mean 3 months	IMPORTANT[b]	⊕◯◯◯ VERY LOW[c,d,e,f,g]
Quality of life assessed with: Stroke and Aphasia Quality of Life Scale-39 Italian Version follow up: mean 3 months	CRITICAL[b]	⊕◯◯◯ VERY LOW[c,d,f]
Quality of life assessed with: World Health Organization Quality of Life Scale	CRITICAL[b]	⊕◯◯◯ VERY LOW[d,h,i]
Neurological function assessed with: Scale for the Assessment and Rating of Ataxia follow up: mean 3 months	IMPORTANT[j]	⊕◯◯◯ VERY LOW[e,f,g,k,l,m,n]
Neurological function assessed with: 9HPT follow up: mean 3 months	IMPORTANT[j]	⊕◯◯◯ VERY LOW[e,f,g,k,m]

Neurological function assessed with: ICARS follow up: mean 3 months	IMPORTANT[j]	⊕◯◯◯ VERY LOW[e,f,k,l,m,o,p]	

a. Identified as critical (3/6) and important (3/6) by people with FA and important by the expert authors for this topic.
b. Identified as critical (1/3) and important (2/3) by people with FA and important by the expert authors for this topic.
c. N=1 with diagnosis of Friedreich ataxia.
d. Single study published.
e. Confidence intervals not reported.
f. Allocation concealment not reported or allocation not concealed from enrolling investigator.
g. Potential for carryover effects in crossover trial/s.
h. Participants had diagnosis of SCA3, MSA-cerebellar type & post-lesion ataxia.
i. No confidence intervals reported with low absolute numbers of participants.
j. Outcome rated as important by both people with FA (3/3) and expert authors for this topic.
k. In patient cohorts only n=3 had a diagnosis of Friedreich ataxia.
l. Clinical scales measuring multiple domains of neurological impairment.
m. Small sample sizes (n<30 per study).
n. Meta-analysis not performed. Positive trends in all studies but CIs not published.
o. The duration and type of neuromodulation varied between studies. Two studies had intervention period of 5 days per week for 2 weeks and one study examined a single session. Two studies examined anodal cerebellar tDCS and one study examined combined anodal cerebellar tDCS and cathodal spinal tDCS.
p. Potential for carryover effects in crossover trial in two studies (Benussi et al 2015 & Benussi et al 2018).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		A survey designed to systematically collect expert-based opinions from clinicians involved in developing the recommendations for this topic and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada, and the USA were asked to consider the harms/benefits of **neuromodulation (i.e. stimulation, tDCS, TMS) as a management strategy for all individuals**. Reflecting on the impact of **neuromodulation (i.e. stimulation, tDCS, TMS)** on Improvement in daily activities, 50% (2/4) clinical experts reported a benefit (large, moderate or small), 25% (1/4) reported no effect and, 0% (0/4) reported observing a harm (large, moderate or small). 1 clinician could not provide any information on this outcome. Reflecting on the impact on Improvement in quality of life, 50% (2/4) clinical experts reported a benefit, 25% (1/4) reported no effect. 1 expert clinician could not provide any information on this outcome. Reflecting on the impact on Neurological function, 75% (3/4) clinical experts reported a benefit. 1 expert clinician could not provide any information on this outcome.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if neuromodulation was acceptable (weighing up the balance between benefits, harms and costs). 1/4 indicated that it was probably reasonable, 2/4 indicated that more information on the benefits and potential harms were required, 1/4 didn't know if it was reasonable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We conditionally recommend considering electrical stimulation (but not tDCS or TMS) for management of upper limb function in individuals with Friedreich ataxia in a clinical setting, with appropriate evaluation prior to treatment.

Justification

Anecdotal observations whilst administering electrical stimulation (ES)/functional electrical stimulation (FES) under trial conditions reinforce the importance of using clinical reasoning to guide the treatment and that the intervention needs to be driven by a suitably qualified clinician. Setting and adjusting the stimulation parameters requires careful consideration and monitoring for fatigue effects. Identification of realistic upper limb functional goals is particularly important.

Subgroup considerations

Pilot data (unpublished) indicates ES/FES may improve upper limb function in individuals with later stage FRDA.

There are well documented contraindications for ES/FES and screening for these indications is part of routine clinical care. Sensation should be comprehensively evaluated prior to commencing ES and skin integrity should be carefully monitored. Access to carer support for the application of ES/FES is essential.

Research priorities

Pilot data supports randomized, controlled studies aimed at verifying the effect of ES/FES on improving upper limb functional capacity in individuals with FRDA.

Preliminary studies in similar conditions (neurodegenerative ataxias of mixed aetiology) support exploration of tDCS and TMS for upper limb management in the FRDA population under research conditions