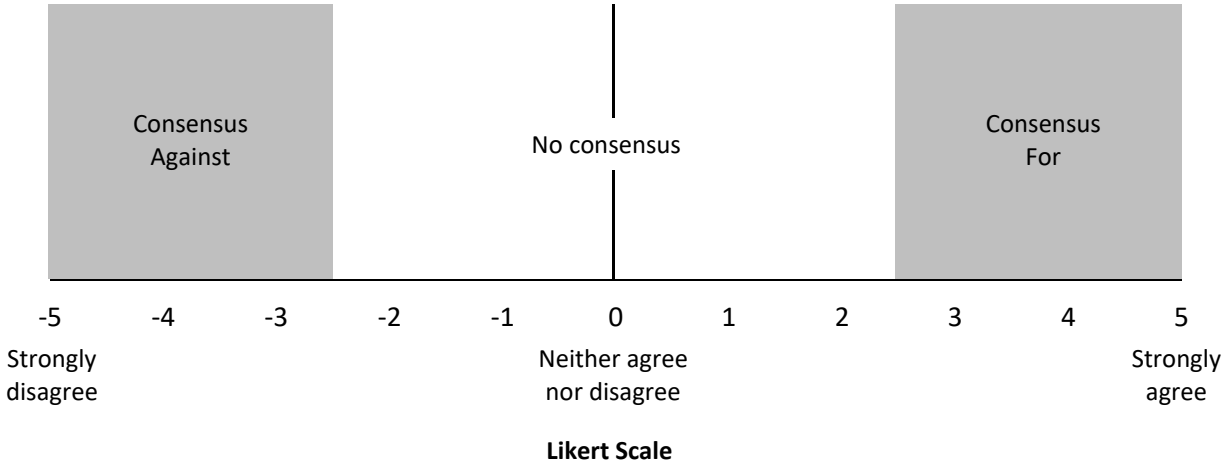
Supplementary Appendix

Appendix 1. The Likert scale and definitions of consensus used throughout the Delphi process.



Appendix 2. RCI Treatment Algorithm Delphi Questionnaire 3 Results

This table contains the questions from the third Delphi questionnaire, the mean and standard deviation of the Likert scale results, and whether consensus was reached or not reached.

Delphi Statement/Question	Mean	Std Dev	Consensus
DOSING			
Since repository corticotrophin injection (RCI) dosing is typically 40–80 units delivered by either intramuscular or subcutaneous injection every 24–72 hours, it is possible to individualize the dosage according to the patient's medical condition as well as disease severity.			
Initiating Therapy			
1. For most pulmonary sarcoidosis patients, the initial RCI dose should be			
1a. 80U sq q72h	−0.4	2.6	No
1b. 80U twice weekly	1.4	2.6	No
1c. 40U daily, titrated down if response occurs	−2.1	2.2	No
1d. 40U three times weekly	0.3	2.9	No
1e. 40U sq q72h	1.0	3.0	No
1f. 40U twice weekly	3.0	2.1	For
2. General dosing issues			
2a. Most patients with less active disease should receive a lower initial RCI dose, eg 40U twice weekly	2.7	2.3	For
2b. Most patients with more active disease should receive a higher initial RCI dose, eg 80U twice weekly	1.1	3.1	No
2c. The initial RCI dose should be determined based on patient body weight	−0.3	2.4	No
3. For patients who have had concerning adverse reactions to other medications, the dose should be decreased to 40U twice weekly	1.3	2.4	No
4. For patients with ocular sarcoidosis, the initial RCI dose should be 80U twice weekly	1.8	2.2	No
5. A loading dose is needed when initiating RCI	−1.5	2.8	No
Maintenance Therapy			
6. RCI should be continued as a maintenance dose for most patients who respond to RCI	3.2	1.8	For
7. RCI should be continued at a maintenance dose for patients with chronic refractory sarcoidosis who respond to RCI	3.5	1.7	For
8. The maintenance dose should be determined individually for each patient	3.2	1.5	For

9. The maintenance dose should be determined by starting at a low RCI dose (eg 40U twice weekly) and titrating up until satisfactory response is achieved	0.5	2.4	No
10. The maintenance dose should be determined by starting at a high RCI dose and titrating down to the lowest effective dose	1.5	1.9	No
Concomitant Steroids			
11. In patients receiving RCI and concomitant steroids, steroids should be tapered or weaned	4.2	1.4	For
12. Weaning or tapering of steroids should be done as rapidly as possible	2.8	2.2	For
13. Weaning or tapering of steroids should be started 2-3 months after initiation of RCI	−1.6	2.9	No
RCI Dose Reduction or Discontinuation			
14. The RCI dose should be reduced or discontinued if			
14a. Excessive RCI-related toxicity develops	4.3	1.4	For
14b. Significant oedema develops	3.3	1.4	For
14c. Hyperglycaemia and/or diabetic complications develop	3.0	1.3	For
14d. Infection develops	2.0	2.5	No
14e. Psychiatric adverse events occur (eg suicidal thoughts, agitation, psychosis)			
14f. Major steroid side effects develop (eg cushingoid features, increased pigmentation)	3.4	1.6	For
14g. RCI-related costs are excessive	2.8	2.0	For
14h. Response to RCI is lost (symptoms or signs progress after an initial response)	3.0	1.7	For
14i. RCI is ineffective in achieving goals of therapy	3.2	1.9	For
15. RCI should be considered ineffective if symptoms or signs do not improve			
15a. Within 1-2 months	−1.8	1.5	No
15b. Within approximately 3 months	1.8	2.7	No
15c. Within 3-6 months	3.3	2.7	For
15d. Within 12 months	2.8	4.0	No
Weaning RCI			
16. The patient should be weaned from RCI if:			
16a. The disease is stable and well-controlled for 3-6 months	0.0	2.6	No
16b. The disease is stable and well-controlled for 6-12 months	3.1	1.7	For
16c. The disease is stable and well-controlled for 1-3 months	−1.3	2.8	No

17. RCI should be weaned by decreasing the dosing frequency, then decreasing the dose, then stopping	2.6	1.9	For
18. RCI should be weaned by gradually decreasing the dose, then stopping	1.4	2.3	No
19. Weaning RCI by decreasing the frequency, then decreasing dose is preferable to weaning by just decreasing the dose	0.0	2.4	No
Route of Administration			
20. For most patients, RCI should be administered by subcutaneous injection	4.0	1.6	For
21. RCI may be administered by intramuscular injection if subcutaneous injection fails	3.1	1.8	For
Testing and Dosing in Special Populations			
22. The following tests should be done (or recent results should be available) before initiating RCI:			
22a. Complete blood count (CBC)	2.7	2.3	For
22b. Comprehensive metabolic panel (CMP)	3.3	2.4	For
22c. Liver function tests	2.5	2.9	No
22d. HbA1C levels	2.3	1.9	No
22e. Bone density scan (DEXA)	2.8	1.7	For
22f. Tuberculosis	2.2	2.8	No
22g. Hepatitis B and C	1.7	2.8	No
22h. HIV	0.8	2.9	No
22i. TSH	1.8	2.7	No
23. Tuberculosis screening before initiating RCI can use the following test(s):			
23a. No specific screening is required	0.8	3.2	No
23b. Screening is only needed if the patient has risk factors, eg history of TB, history of TB exposure, or on relevant concomitant medications	1.0	2.7	No
23c. Close monitoring with no specific test	0.3	2.7	No
23d. Tuberculin	−0.2	2.9	No
23e. Interferon gamma	0.2	3.6	No
23f. Quantiferon Gold	2.1	2.9	No
23g. Chest x-ray	1.5	3.1	No
23h. Please list any other appropriate TB screening tests	−1.1	2.4	No
23i. No specific screening is required	−1.0	3.1	No
24. The following conditions are contraindications to RCI:			
24a. Latent TB	1.3	2.2	No
24b. Hypothyroidism	−0.7	2.6	No

24c. Decompensated cirrhosis	1.1	2.7	No
24d. Any cirrhosis	−0.5	2.3	No
24e. Primary adrenocortical insufficiency	2.3	1.7	No
24f. Adrenocortical hyperfunction	1.9	2.2	No
24g. Untreated osteoporosis	1.1	2.2	No
24h. Any osteoporosis	−0.2	2.6	No
24i. Uncontrolled systemic fungal infection	4.0	1.4	For
24j. Any systemic fungal infection	2.5	1.7	No
24k. Uncontrolled ocular herpes simplex infection	3.8	1.4	For
24l. Any ocular herpes simplex infection	2.1	2.4	No
24m. Recent surgery	0.4	2.5	No
24n. Treated/controlled peptic ulcer	−1.2	2.4	No
24o. Any peptic ulcer	−0.2	2.2	No
24p. Decompensated / uncontrolled congestive heart failure	1.8	2.0	No
24q. Any congestive heart failure	0.0	2.0	No
24r. Uncontrolled hypertension	1.0	2.4	No
24s. Any hypertension	−1.2	2.2	No
24t. Scleroderma	0.8	3.2	No
24u. Sensitivity to proteins of porcine origin	3.8	1.5	For
24v. Severe or brittle diabetes	2.9	1.7	For
24w. Insulin requiring diabetes	1.3	2.1	No
24x. Patient difficulty with or dislike of self-injection	1.7	2.1	No
24y. Pre-existing osteoporosis and hypertension are acceptable if monitored and the patient is on medication for these conditions	2.1	3.2	No

Adverse Effect Management

Effective management of the adverse events (AE) associated with RCI is important to promote adherence and thereby improve outcomes. However, little or no published guidance on AE management is available. This portion of the questionnaire focuses on the prevention and management of common and/or important RCI-related adverse events.

Note that many AEs associated with RCI, particularly near the time of RCI administration, are similar to those associated with high-dose steroids. In answering the following questions, please focus on RCI-specific AEs.

Oedema

25. Non-Pharmacological Management of new/worsening oedema should include			
25a. Evaluate/diagnose potential causes	4.4	1.4	For
25b. Limit salt intake	4.0	1.5	For

25c. Elevation	3.7	1.4	For
26. Pharmacological Management of new/worsening oedema should include			
26a. Initiate diuretics	3.6	1.6	For
26b. Loop diuretics (Lasix, etc.)	2.9	1.9	For
26c. Spironolactone (Aldactone)	2.8	1.9	For
27. RCI Dose Adjustment			
27a. Dose down titration after pharmacological and non-pharmacological interventions fail	3.6	1.4	For
27b. Dose down titration concomitant to pharmacological and non-pharmacological interventions due to severity of AE	2.9	1.6	For
27c. Medication discontinuation if other interventions fail	3.0	2.4	For
27d. Medication discontinuation if AE is severe and significant	4.3	1.5	For
27e. Re-up titration or resumption of medication at lower dose once symptoms resolve	2.4	1.7	No
Anxiety/Depression			
28. Non-Pharmacological Management of new/worsening anxiety/depression should include			
28a. Refer to PCP/psychiatry	2.7	2.6	For
29. Pharmacological Management of new/worsening anxiety/depression should include			
29a. Anxiolytic therapy	1.0	1.6	No
29b. Anti-depressant therapy (eg SSRI)	1.8	1.8	No
29c. Antipsychotic medication	−0.7	2.3	No
30. RCI Dose Adjustment			
30a. Dose down titration after pharmacological and non-pharmacological interventions fail	3.5	1.6	For
30b. Dose down titration concomitant to pharmacological and non-pharmacological interventions due to severity of AE	3.5	1.6	For
30c. Medication discontinuation if other interventions fail	4.1	1.6	For
30d. Medication discontinuation if AE is severe and significant	4.3	1.5	For
30e. Re-up titration or resumption of medication at lower dose once symptoms resolve	0.7	2.7	No
Infection			
31. Pharmacological Management of Infection should include			
31a. First-line treatment of the specific infection	4.4	1.5	For

31b. Second-line treatment of the specific infection	3.5	1.7	For
31c. Switch to IV steroid from Acthar gel	−0.5	2.0	No
31d. Steroids are only used if there is concern about adrenal insufficiency or patient had severe organ (life threatening) disease	1.9	1.7	No
32. RCI Dose Adjustment			
32a. Dose down titration after pharmacological interventions fail	2.4	3.0	No
32b. Dose down titration concomitant to pharmacologic interventions due to severity of AE	3.8	1.5	For
32c. Medication discontinuation if other interventions fail	3.9	1.5	For
32d. Medication discontinuation if AE is severe and significant	4.2	1.5	For
32e. Re-up titration or resumption of medication at lower dose once symptoms resolve	2.3	2.0	No
Increased appetite/weight gain			
33. Non-Pharmacological Management if the patient develops increased appetite and weight gain should include			
33a. Behavioural intervention	4.3	1.5	For
33b. Dietary counselling	4.2	1.5	For
33c. Exercise program	4.1	1.4	For
33d. Pulmonary rehabilitation	3.5	1.9	For
34. Pharmacological Management if the patient develops increased appetite and weight gain should include			
34a. First line—Appetite suppressants	−0.5	3.5	No
34b. Second line—Appetite suppressants	−1.3	3.1	No
34c. Shorten the counselling interval	0.4	3.5	No
35. RCI Dose Adjustment			
35a. Dose down titration after pharmacological and non-pharmacological interventions fail	2.9	1.6	For
35b. Dose down titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	3.4	1.8	For
35c. Medication discontinuation if other interventions fail	3.3	1.7	For
35d. Medication discontinuation if AE is severe and significant	4.0	1.5	For
35e. Re-up titration or resumption of medication at lower dose once symptoms resolve	1.6	1.6	No
Glucose intolerance/worsening in glucose control			

36. Pharmacological Management if the patient develops glucose intolerance/worsening in glucose control should include			
36a. Manage glucose with metformin	2.3	1.5	No
36b. Manage glucose with insulin	2.3	1.4	No
36c. Manage glucose with other oral agents	2.2	1.3	No
36d. Same as with oral steroids	3.0	1.4	For
37. RCI Dose Adjustment			
37a. Dose down titration after pharmacological interventions fail	3.1	1.3	For
37b. Dose down titration concomitant to pharmacologic interventions due to severity of AE	3.1	1.6	For
37c. Medication discontinuation if other interventions fail	3.0	1.7	For
37d. Medication discontinuation if AE is severe and significant	3.9	1.6	For
37e. Re-up titration or resumption of medication at lower dose once symptoms resolve	1.8	1.8	No
Hypertension			
38. Non-Pharmacological Management if the patient develops hypertension should include			
38a. Educate on sodium and fluids	4.3	1.4	For
38b. Refer to PCP	3.5	1.9	For
39. Pharmacological Management if the patient develops hypertension should include			
39a. First line—Antihypertensive medication	3.7	1.5	For
39b. Second line—Add or increase antihypertensive medication	3.1	1.3	For
40. RCI Dose Adjustment			
40a. Dose down titration after pharmacological and non-pharmacological interventions fail	3.1	1.6	For
40b. Dose down titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	3.6	1.4	For
40c. Medication discontinuation if other interventions fail	3.3	1.5	For
40d. Medication discontinuation if AE is severe and significant	3.8	1.7	For
40e. Re-up titration or resumption of medication at lower dose once symptoms resolve	1.7	1.7	No
Darkening of the Skin			
41. Non-pharmacological and pharmacological management if the patient develops darkening of the skin should include			

41a. Counselling for patient	4.1	1.5	For
41b. Topical skin therapies	2.3	2.2	No
42. RCI Dose Adjustment			
42a. Dose down titration after pharmacological and non-pharmacological interventions fail	2.7	1.9	For
42b. Dose down titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	3.0	2.5	For
42c. Medication discontinuation if other interventions fail	2.5	1.7	No
42d. Medication discontinuation if AE is severe and significant	3.7	1.3	For
42e. Re-up titration or resumption of medication at lower dose once symptoms resolve	0.5	2.6	No
Other Skin-related AEs			
43. Non-pharmacological interventions if the patient develops other skin-related AEs should include			
43a. Refer to dermatology	2.5	2.6	No
43b. Counselling; encourage patient to complete the course of therapy	3.3	2.3	For
43c. Rotate the injection site	3.8	1.5	For
44. Pharmacological interventions if the patient develops other skin-related AEs should include			
44a. First line—topical skin therapies	3.2	1.7	For
44b. Second line—reduce RCI dose or frequency	2.8	1.4	For
44c. Refer to dermatology	3.1	1.8	For
45. RCI Dose Adjustment			
45a. Dose down-titration after pharmacological and non-pharmacological interventions fail			Not asked
45b. Dose down titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	2.7	2.1	For
45c. Medication discontinuation if other interventions fail	1.8	2.1	No
45d. Medication discontinuation if AE is severe and significant	3.9	1.6	For
45e. Re-up titration or resumption of medication at lower dose once symptoms resolve	2.1	1.8	No
Localized injection site pain			
46. Non-pharmacological management for localised injection site pain should include			
46a. Cool skin with an ice pack	4.1	1.5	For

46b. Rotate injection sites	4.3	1.5	For
46c. Slower injection rate	3.4	1.8	For
46d. Educate on injection technique	4.3	1.4	For
46e. Massage the area	2.8	2.1	For
47. Pharmacological management for localised injection site pain should include			
47a. Local anaesthetics (lidocaine/EMLA)	0.7	2.0	No
47b. Ibuprofen	2.2	1.5	No
48. RCI Dose Adjustment			
48a. Dose down titration after pharmacological and non-pharmacological interventions fail	1.3	1.1	No
48b. Dose down titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	2.6	1.4	For
48c. Medication discontinuation if other interventions fail	2.4	1.4	No
48d. Medication discontinuation if AE is severe and significant	3.7	1.4	For
48e. Re-up titration or resumption of medication at lower dose once symptoms resolve	2.5	1.7	No
Insomnia			
49. Non-pharmacological management for insomnia should include			
49a. Sleep hygiene	4.2	1.4	For
49b. Mindfulness techniques/meditation	4.0	1.5	For
50. Pharmacological management for insomnia should include			
50a. OTC (eg Benadryl, melatonin)	3.5	1.5	For
50b. Ambien (zolpidem)	1.8	2.6	No
50c. Remeron (mirtazapine)	2.0	2.0	No
50d. Trazodone	1.1	2.4	No
50e. Lunesta (eszopiclone)	1.3	2.6	No
50f. Klonopin (clonazepam)	0.6	2.4	No
50g. Antidepressant or anxiolytics depending on symptoms	0.8	2.4	No
50h. Integrative medicine	3.0	1.8	For
51. RCI Dose Adjustment			
51a. Dose down-titration after pharmacological and non-pharmacological interventions fail	2.0	1.5	No
51b. Dose down-titration concomitant to pharmacologic and non-pharmacological interventions due to severity of AE	2.8	1.7	For

51c. Medication discontinuation if other interventions fail	2.8	2.0	For
51d. Medication discontinuation if AE is severe and significant	3.6	1.7	For
51e. Re-up titration or resumption of medication at lower dose once symptoms resolve	1.8	1.9	No
Concomitant immunosuppressive medications			
52. Management of concomitant immunosuppressive medications should include			
52a. Monitor as when using steroids	3.8	1.5	For
52b. Standard of care with the appropriate laboratory and adverse effect management	4.5	1.5	For
52c. Continue methotrexate or Imuran	4.0	1.5	For
52d. Attempt to reduce dose as tolerated; starting with prednisone, then other immunosuppressive medications, then RCI	2.3	2.3	No
52e. Use RCI to maintain immunosuppression until a concomitant immunosuppressant is on board	3.1	1.5	For
52f. Decrease immunosuppressant dose if possible depending on which medications are used	2.6	1.8	For
52g. Keep DMARDs unchanged while taking RCI	3.2	1.6	For
52h. Maintain dosage unless and until goals are met	3.5	1.4	For
52i. Decrease the dose of concomitant medications	0.1	2.6	No
53. RCI Dose Adjustment			
53a. Dose down titration after concomitant immunosuppressive medications fail	0.6	2.5	No
53b. Dose down titration concomitant to immunosuppressive medications due to severity of AE	2.0	2.3	No
53c. Medication discontinuation if concomitant immunosuppressive medications fail	0.3	2.5	No
53d. Medication discontinuation if AE is severe and significant	3.1	1.6	For
53e. Re-up titration or resumption of medication at lower dose once symptoms resolve	1.8	1.5	No
Hospitalisation			
54. Management when patients are hospitalised should include			
54a. Ensure patient receives steroids at a stress dose	3.1	1.9	For
54b. Hold RCI dose	0.8	2.6	No
54c. Continue RCI	0.4	3.2	No
Continue RCI unless hospitalisation is for	−0.7	4.0	No
54d. Infection	1.5	3.1	No

54e. Life-threatening infection	3.4	3.0	For
54f. Heart failure	1.7	3.3	No
54g. Hyperglycaemia	1.8	3.3	No
54h. Surgery	1.1	3.3	No
54i. Sepsis	3.2	2.9	For
54k. Continue to hold RCI until discharge	0.7	3.6	No
54l. Hold RCI if any questionable RCI-related cause	3.3	2.9	For
54m. Stop RCI if needed due to severe exacerbations such as neurosarcoidosis related issues	2.3	2.4	No

Treatment Practice-specific questions

Note: these questions did not seek consensus

Of the patients with pulmonary sarcoidosis you have treated with RCI,

55. What percent were started on RCI because of **intolerance** to steroids, cytotoxic agents or biologics?	30%	25.41
56. What percent (%) were started on RCI as **second line** to steroids?	36%	37.47
57. What percent (%) were started on RCI as **third line: Combination** of steroids **AND** cytotoxic agents failed?	28%	21.62
58. What percent were started on RCI as **third line**: **Combination** of steroids **AND** biologics failed?	16%	13.90
59. What percent were started on RCI as **fourth line** therapy: **Combinations** of steroids/cytotoxics and biologics, tried and failed?	14%	14.00

60. When treating for pulmonary sarcoidosis with steroids, cytotoxic agents and biologics, how have you typically paired RCI in combination with these agents?

- Yes
- Usually RCI instead of biologic
- Just added on, then starting tapering steroids rather quickly
- Determine whether patient is benefiting from the combination of drugs. Usually RCI is for advanced, refractory patients.
- RCI+cytotoxic agents
- Steroids, then MTX, then RCI or infliximab
- Have not used this pairing
- If concerned patient constitution not robust enough for steroids, eg HIV, myositis with fear of not weaning from steroids rapidly etc. Steroids and steroid type medications are for quick onset to quell a fire and with simultaneous transition to steroid -sparing agent.
- Similar to corticosteroid use, I pair with MTX or azathioprine or even infliximab.
- Often start the RCI and wean the others
- I start 40 twice weekly in addition to the current steroid dose and MTX or others, I uptitrate the dose if the BP and blood sugar are maintained

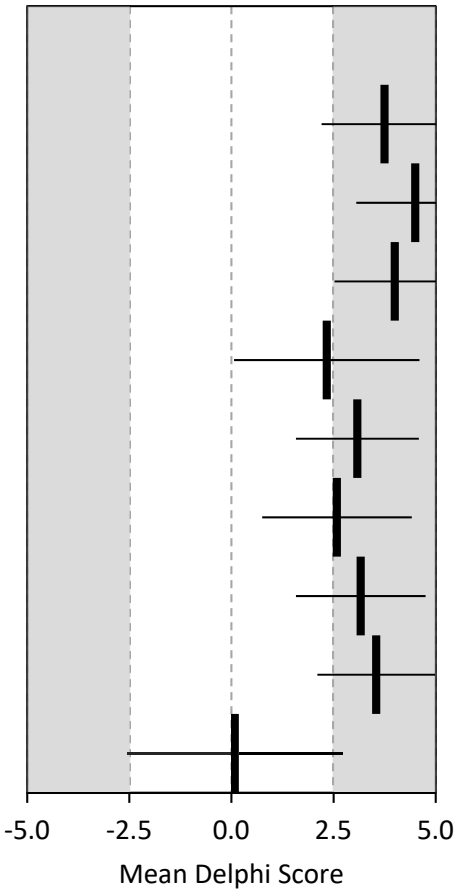
- No specific pairings

61. Are there any patient populations or treatment settings where RCI may be appropriate to use concomitantly?

- Most patients using cytotoxic agents as sole therapy may benefit from RCI therapy as concomitant meds
- Patients failing biologics but who still have evidence for inflammation (e.g. positive PET scan)
- Refractory sarcoidosis with progressive decline
- Severe systemic disease such as patients with eye, lung, liver and spleen and bone involvement
- Probably, I just have not
- Concomitantly with steroids? No, only when trying to wean steroids. We don't have these answers yet. I use in HIV patients mostly instead of steroids though there is no good data for this- just hoping for a better, more protective outcome - but it's been a long time
- Not sure
- Severe progressive sarcoidosis
- Appropriate treatment of refractory disease

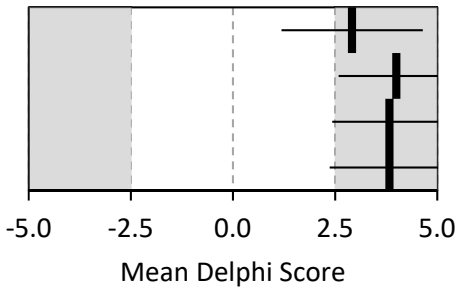
Appendix 3. Consensus recommendations for managing concomitant immunosuppressive medications in patients receiving RCI as therapy for pulmonary sarcoidosis.

Management strategy	Mean	Std Dev
Management of concomitant immunosuppressive medications should include		
Monitor as when using steroids	3.8	1.5
Standard of care with the appropriate laboratory and adverse effect management	4.5	1.5
Continue methotrexate or azathioprine	4.0	1.5
Attempt to reduce dose as tolerated; starting with prednisone, then other immunosuppressants	2.3	2.3
Use RCI to maintain immunosuppression until a concomitant immunosuppressant is on board	3.1	1.5
Decrease immunosuppressant dose if possible depending on which medications are used	2.6	1.8
Keep DMARDs unchanged while taking RCI	3.2	1.6
Maintain dosage unless and until goals are met	3.5	1.4
Decrease the dose of concomitant medications	0.1	2.6



Appendix 4. Consensus recommendations for contraindications to RCI therapy in pulmonary sarcoidosis.

Contraindication	Mean	Std Dev
Severe or brittle diabetes	2.9	1.7
Uncontrolled fungal infection	4.0	1.4
Uncontrolled ocular herpes simplex virus infection	3.8	1.4
Sensitivity to porcine proteins	3.8	1.5



Appendix 5. Consensus recommendations for use of RCI as therapy for pulmonary sarcoidosis in hospitalised patients.

Statement	Mean	Std Dev
Management of hospitalised patients should include:		
Hold RCI if any questionable RCI-related cause	3.3	2.9
Ensure patient receives steroids at a stress dose	3.1	1.9
Continue RCI unless hospitalisation is for:		
Life-threatening infection	3.4	3.0
Sepsis	3.2	2.9