Clinical Priorities Advisory Group
4 December 2024

Agenda Item No	2.1
National Programme	Blood and Infection
Clinical Reference Group	Specialised Immunology and Allergy
URN	2319

Title
Etanercept and adalimumab for the treatment of deficiency of adenosine deaminase type 2 (aged 5 years and older)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Etanercept and adalimumab are both recommended to be available as routine commissioning treatment options for deficiency of adenosine deaminase type 2 (DADA2). DADA2 is a rare, inherited disorder characterised by abnormal inflammation, and immune system dysfunction. Vasculitis is one of the most predominant features of DADA2 and often begins early in childhood, with many patients experiencing early-onset strokes or peripheral vascular disease before the age of 10. Etanercept and adalimumab are both from the anti-tumour necrosis factor (TNF) drug class. Both drugs are used to prevent further strokes and to maintain remission in this condition. This proposed use of both etanercept and adalimumab is off label. The policy proposition is restricted to adults and children aged five years and over in line with the findings from the evidence review. Children aged 2-4 years can access this treatment via the Commissioning Medicines for Children policy in line with licenced indications for both etanercept and adalimumab. There is insufficient safety evidence to use either drug in children younger than 2 years old. Specialised rheumatology services are jointly commissioned (delegated service ready and suitable for greater ICS leadership). Specialised immunology services are suitable and ready for delegation from April 2025.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

Etanercept monotherapy for deficiency of adenosine deaminase 2 (DADA2)

In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness and safety of etanercept compared with standard care?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Number of ischaemic events **Certainty of evidence:** Very low	This is an important outcome to patients as ischaemic events are a detrimental effect of DADA2 and prevention of ischaemic events is an indication of successful treatment. Four retrospective case series provided non-comparative evidence relating to ischaemic events in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[1]. One retrospective case series reported the number of patients with neurological symptoms for the one year follow-up after initiation of etanercept. Three retrospective case series reported the number of patients with ischaemic events (including stroke) at a median of 20.2

[1] Baseline defined as before the initiation of etanercept. Treatments received before the initiation of etanercept varied widely between studies.

Outcome	Evidence statement
	months follow-up after diagnosis of DADA2, after median 74 months, or between two months and >10 years after treatment with etanercept. MRI-confirmed strokes after adequate disease control (not defined) **At follow-up of the whole cohort between two months and >10 years:[2]** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 6 of 7 (85.7%) patients with DADA2 had MRI-confirmed strokes prior to treatment with etanercept. After adequate disease control (not defined) with etanercept, none of the 7 (0%) patients experienced an MRI-confirmed stroke. No statistical measures were reported. **(VERY LOW)** Neurological symptoms **At one-year follow-up:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that 1 patient with DADA2 had neurological symptoms prior to treatment with etanercept. The same patient was described as *"neurologically symptom-free"* after initiation of etanercept.[3] No further details were provided and no statistical measures were reported. **(VERY LOW)** Stroke/stroke activity **At median 20.2 months follow-up after diagnosis of DADA2:[4]** • One retrospective case series (Li et al 2023) (n=13) reported that *"… no patients have had a stroke during the time they have been on treatment"*. No further details were provided and no statistical measures were reported. **(VERY LOW)** Ischaemic events **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that 5 of 5 (100%) patients with DADA2 reported experiencing a total of 11 CNS ischaemic events prior to treatment with etanercept. After initiation of etanercept, none of the 5 patients (0%) had experienced a CNS ischaemic event. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=5) reported that 2 of 5 (40%) patients with DADA2 reported experiencing one non-CNS ischaemic event each prior to treatment with etanercept. After initiation of etanercept, 1 of 5 (20%) patients had experienced a non-CNS ischaemic event[5] (one patient who had events before etanercept). No statistical measures were reported. **(VERY LOW)**

[2] Duration of follow-up of etanercept patients not stated.
[3] No comments relating to ischaemic events after etanercept were made for the remaining four patients.
[4] Follow-up period for full cohort of 30 patients. Follow-up duration for 13 patients receiving etanercept was not available separately.
[5] One patient developed digital necrosis resulting in a partial amputation due to poor compliance with etanercept. This patient had both CNS and non-CNS ischaemic events before treatment with etanercept.

Outcome	Evidence statement
	Four retrospective case series provided very low certainty evidence on ischaemic events in patients with DADA2. All four case series reported reductions in the number of patients with DADA2 who experienced ischaemic events (including CNS and non-CNS strokes) after initiation of etanercept, compared to baseline. Follow-up durations varied between one year follow-up, a median of 20.2 months after diagnosis of DADA2, after median 74 months, or was described for the whole cohort between two months and >10 years. No statistical measures were reported.
Disease activity/response **Certainty of evidence:** Very low	This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of DADA2, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression. Seven retrospective case series provided non-comparative evidence relating to disease activity/response in patients with DADA2 after initiation of etanercept. All seven case series reported results compared to baseline[1]. Disease activity/response was defined differently across the studies, including using the PVAS, or defined as number of patients in clinical remission or having complete control of disease. Follow-up durations varied, including the next 9 months of treatment, at a median of 20.2 months after diagnosis of DADA2, or at median 23 months to after 74 months. **During the next 9 months of etanercept treatment:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that for 1 patient with DADA2, etanercept resulted in *"complete remission of the disease for the next 9 months"* (not further defined).[6] No further details were provided and no statistical measures were reported. **(VERY LOW)** **At follow-up of the whole cohort between two months and >10 years:[2]** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had anaemia before treatment with etanercept. After initiation of etanercept 1 of 7 (14.3%) patients had anaemia (the same patient with anaemia prior to treatment). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had lymphopenia before treatment with etanercept. After initiation of etanercept 1 of 7 (14.3%) patients had lymphopenia (the same patient with lymphopenia prior to treatment). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 4 of 7 (57.1%) patients with DADA2 had hypogammaglobulinemia before treatment with etanercept. After initiation of etanercept 4 of 7 patients (57.1%) had

[6] No comments relating to disease activity/response after etanercept were made for the remaining four patients.

Outcome	Evidence statement
	hypogammaglobulinemia (the same patients with hypogammaglobulinemia prior to treatment). No statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[4]** • One retrospective case series (Li et al 2023) (n=13) reported that before etanercept, no patients were in complete or partial remission. After initiation of etanercept, 12 of 13 (92.3%) patients with DADA2 had complete remission[7] and 1 of 13 (1.7%) patients with DADA2 had partial remission[8] . No statistical measures were reported. **(VERY LOW)** **At median 23 months follow-up:** • One retrospective case series (Celikel et al 2023) (n=6) reported that 6 of 6 (100%) patients with DADA2 were in clinical remission[9] after initiation of etanercept. The authors stated that *"after the initiation of [etanercept], clinical findings improved and inflammation was suppressed in 6 patients".* No statistical measures were reported. **(VERY LOW)** **At median 3.5 years follow-up:** • One retrospective case series (Kasap Cuceoglu et al 2021) (n=18) reported that 17 of 18 (94.5%) patients with DADA2 were in complete remission (not further defined) after initiation of etanercept. The authors also stated that 3 of 18 (16.7%) patients relapsed during follow-up.[10] No statistical measures were reported. **(VERY LOW)** **At median 56 months follow-up:** • One retrospective case series (Melo et al 2023) (n=9) reported that all 9 patients (100%) with DADA2 had complete control of disease[11] after initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:**

[7] Defined as persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment.
[8] Defined as good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage.
[9] Clinical remission defined as the absence of active vasculitis, recovery/stabilisation of disease-related organ damage and absence of systemic inflammation. Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.
[10] It was unclear what the sequence of events was as to when patients relapsed, when they were in remission and when the patient died as no further details were reported.
[11] Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.

Outcome	Evidence statement
	• One retrospective case series (Cooray et al 2021) (n=5) reported that the median PVAS[12] was 29 (IQR 21 to 30) in patients with DADA2 before treatment. After initiation of etanercept, the PVAS reduced to 1 (IQR 0 to 2), indicating improvement. No statistical measures were reported. **(VERY LOW)** **Seven retrospective case series provided very low certainty evidence on disease activity/response in patients with DADA2. Four retrospective case series reported that between 92.3% and 100% patients with DADA2 were in remission (defined differently across studies) or had complete control of disease after initiation of etanercept at median 20.2 months after diagnosis of DADA2 or between a median of 23 and 56 months follow-up, compared to baseline. One retrospective case series reported that, compared to baseline, patients with DADA2 did not show improvements in anaemia, lymphopenia, and hypogammaglobulinemia at follow-up of the whole cohort between two months and >10 years. One retrospective case series reported improvements in median PVAS after median 74 months follow-up, compared to baseline.**
Symptom alleviation **Certainty of evidence:** Very low	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. Six retrospective case series provided non-comparative evidence relating to symptom alleviation (defined as resolution of symptoms, symptom alleviation after initiation of etanercept, or patients with individual symptoms such as seizures) in patients with DADA2 after initiation of etanercept. All six case series reported results compared to baseline[1]. Follow-up durations were at 3 months after initiation of etanercept, at one year follow-up, at median between one year, or at follow-up of the whole cohort between two months and >10 years. Systemic inflammation (not defined) **At 3 months after initiation of etanercept:** • One retrospective case series (Tanatar et al 2020) (n=5) reported that 4 of 5 (80%) patients with DADA2 had systemic inflammation before treatment with etanercept, and this resolved in all 4 (100%) patients at three months after treatment with etanercept. No statistical measures were reported. **(VERY LOW)** Resolution of symptoms **At 3 months after initiation of etanercept:** One retrospective case series (Tanatar et al 2020) (n=5) reported that *"at the 3rd month of etanercept treatment, all the symptoms resolved"* in patients with DADA2. All patients had at least one

[12] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept.

Outcome	Evidence statement
	symptom before treatment. No further details were provided and no statistical measures were reported. (**VERY LOW**) Symptom alleviation **At follow-up of whole cohort between two months and >10 years:**[2] • One retrospective case series (Andriessen et al 2023) (n=7) reported that 5 of 7 (71.4%) patients with DADA2 had cutaneous involvement (except eczema) before treatment with etanercept. After initiation of etanercept none of 7 patients had cutaneous involvement (except eczema). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had eczema before treatment with etanercept. After initiation of etanercept, 3 of 7 (42.8%) patients had eczema including one patient with pre-existing eczema. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 2 of 7 (28.6%) patients with DADA2 had fever before treatment with etanercept. After initiation of etanercept no patients had fever. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 4 of 7 (57.1%) patients with DADA2 had PAN-like rash or other cutaneous vasculitis before treatment with etanercept. After initiation of etanercept no patients had PAN-like rash or other cutaneous vasculitis. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 2 of 7 (28.6%) patients with DADA2 had arthralgia/arthritis[13] before treatment with etanercept. After initiation of etanercept 1 of 7 patients 14.3%) had arthralgia/arthritis (one patient with pre-existing arthralgia/arthritis). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 3 of 7 (42.9%) patients with DADA2 had aphthous stomatitis before treatment with etanercept. After initiation of etanercept no patients had aphthous stomatitis. No statistical measures were reported. **(VERY LOW)** **At median time on etanercept treatment of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[14]) reported that 2 of 9 (22.2%) patients with DADA2 had mild flare with fever prior to treatment with etanercept. Both patients were reported to be *"clinically well"* after initiation of etanercept. No

[13] Spelled as 'artritis' in the paper; assumed to be arthritis

[14] Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients.

Outcome	Evidence statement
	further details were provided and no statistical measures were reported. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=9[14]) reported that before treatment with etanercept, 1 of 9 (11.1%) patients with DADA2 had some livedo. After initiation of etanercept, the same patient had minimal livedo and Raynaud's. No further details were provided and no statistical measures were reported. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=9[14]) reported that after the initiation of etanercept, 1 patient was *"clinically well"* but with some pancytopenia, and 1 patient was *"clinically well"* but some gait disorders remained. Symptoms before starting treatment were not reported for these two patients and no further details were provided. **(VERY LOW)** **At one year after the initiation of etanercept:** One retrospective case series (Kisla Ekinci et al 2022) (n=5[15]) reported that 2 of 5 patients (40%) had complete resolution of symptoms (skin symptoms in n=2, fever in n=1, inflammatory attacks in n=1) after initiation of etanercept; 2 of 5 patients (40%) had improvement in symptoms (skin symptoms in n=2, musculoskeletal in n=1, constitutional symptoms in n=1); and for 1 of 5 patients (20%) (the patient described as being in complete remission) no comment on symptomatic involvement was made. No statistical measures were reported. **(VERY LOW)** Number of seizures **At median 23 months follow-up:** One retrospective case series (Celikel et al 2023) (n=6) reported that 2 of 6 (33.3%) patients with DADA2 had seizures before treatment with etanercept. After initiation of etanercept, 1 patient (16.7%) experienced seizures but it was not clear if this patient had experienced seizures before initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **Six retrospective case series provided very low certainty evidence that, compared to baseline, symptoms generally improved or resolved in patients with DADA2 after initiation of etanercept at 3 months after initiation of etanercept, at one year follow-up, at median follow-up between one year and at median 23 months, or follow-up of the whole cohort between two months and >10 years. Details were mainly presented narratively and no statistical measures were reported.**
Important outcomes	
Steroid use reduction	This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including

[15] No comment on symptomatic involvement was made for one patient. The patient was described as experiencing symptoms before etanercept.

Outcome	Evidence statement
Certainty of evidence: Very low	osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders. Four retrospective case series provided non-comparative evidence relating to steroid use reduction in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[1]. Follow-up durations were between the next 9 or 12 months of etanercept treatment, after median time on etanercept treatment of one year, at median 20.2 months follow-up after diagnosis of DADA2, or after median 74 months. **During the next 9 or 12 months follow-up:** One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that treatment with etanercept resulted *"in cessation of systemic steroids and methotrexate"* in one patient.[16] No further details were provided and no statistical measures were reported. **(VERY LOW)** **After median time on etanercept treatment of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[17]) reported that 3 patients who were treated with etanercept were receiving steroids (prednisone, dose not stated) before anti-TNF inhibitor treatment. After initiation of etanercept, all patients discontinued steroids; 1 patient was receiving hydroxychloroquine, anakinra, and IVIG in addition to etanercept. No further details were provided and no statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[4]** • One retrospective case series (Li et al 2023) (n=13) provided information in a table suggesting that 12 of the 13 patients (92.3%) who received etanercept were receiving glucocorticoids (dose not stated) before anti-TNF inhibitor treatment. After initiation of etanercept, 5 of the 13 patients (38.5%) were on glucocorticoids; the remaining 7 patients on glucocorticoids before initiation of etanercept discontinued glucocorticoid treatment. The authors note that the glucocorticoids had *"little effect"* on DADA2 symptoms. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** One retrospective case series (Cooray et al 2021) (n=5) reported that 4 of 5 (80%) patients received steroids prior to treatment with etanercept and 1 of 5 (20%) patients continued to receive steroids after initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence that steroid use was discontinued in all or nearly all patients with DADA2 after initiation of etanercept compared to**

[16] No comments relating to steroid use reduction after etanercept were made for the remaining four patients.
[17] Information on treatment both before and after commencing treatment with etanercept was available for four patients.

Outcome	Evidence statement
	baseline, with one case series suggesting that glucocorticoids had *"little effect"* on DADA2 symptoms. Follow-up durations were between the next 9 or 12 months of etanercept treatment, after median time on etanercept treatment of one year, at median 20.2 months follow-up after diagnosis of DADA2, or after median 74 months follow-up. Details were limited and not always reported for all patients, and no statistical measures were reported.
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** Not applicable	This outcome is important for patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life ad inform their treatment decision making. **No evidence was identified for this outcome.**
Change in acute phase reactants **Certainty of evidence:** Very low	This outcome is important to patients as normalisation of acute phase reactants is associated with a reduction in symptoms and improved quality of life for patients. This is particularly important in children as normalisation of acute phase reactants in linked to improvements in growth. Four retrospective case series provided non-comparative evidence relating to change in acute phase reactants (i.e. normal APR, CRP, ESR, SAA) in patients with DADA2 after treatment with etanercept. All four case series reported results compared to baseline[1]. Follow-up durations were at 3 months, after median time on etanercept of one year, at median 20.2 months after diagnosis of DADA2 and after median 74 months. <u>Normal APRs (not defined)</u> **At 3 months follow-up:** One retrospective case series (Tanatar et al 2020) (n=5) reported that *"at the 3rd month of etanercept treatment,… <u>APRs</u> were normal"*. No further details were provided and statistical measures were not reported. (**VERY LOW**) <u>Change in CRP levels</u> **After median time on etanercept of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[18]) reported an improvement in <u>CRP levels</u>[19] in patients with DADA2 after initiation of etanercept, reflected in the reduction in median CRP levels from 50.3 mg/L (IQR 33.5 to 56.4; n=4 patients) to

[18] CRP levels were not available in five patients before etanercept or in two patients after initiation of etanercept.
[19] Normal CRP levels were defined as 0.00 to 4.99 mg/L.

Outcome	Evidence statement
	0.35 mg/L (IQR 0.2 to 0.4; n=7 patients). No statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[4]** • One retrospective case series (Li et al 2023) (n=13) reported that 12 of 13 (92.3%) patients with DADA2 had elevated CRP levels at presentation, all were within the normal reference range after initiation of etanercept. Improvements were also reflected in the reduction in median CRP levels from 33.4 mg/L (IQR 18 to 60) to 5.7 mg/L (IQR 4.9 to 6.5) at. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that 4 of 5 patients with DADA2 in whom data were available before etanercept had elevated CRP levels[20]. After initiation of etanercept, data were available for all 5 patients which indicated that CRP levels improved and 4 patients were within normal reference range. Improvements were reflected in the reduction in median CRP levels from baseline: 65 mg/L (IQR 45.5 to 95) to 3 mg/L (IQR 1.8 to 4.5).[21] No statistical measures were reported. **(VERY LOW)** Change in ESR levels **At median 20.2 months follow-up after diagnosis of DADA2:[4]** • One retrospective case series (Li et al 2023) (n=13) reported that 9 of 13 (69.2%) patients with DADA2 had elevated ESR levels before treatment with etanercept, all were within the normal reference range after initiation of etanercept. Improvements were also reflected in the reduction in ESR levels from baseline of 38.5 mm/hr (IQR 19 to 51) to 10 mm/hr (IQR 8 to 13). No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=3) reported that 3 of 5 patients with DADA2 in whom data were available before etanercept had elevated ESR levels.[22] After initiation of etanercept, data were available for 2 patients which indicated that ESR levels improved and 1 patient was within normal reference range. Improvements in ESR levels in patients with DADA2 after initiation of etanercept were reflected in the reduction in median ESR levels from baseline: 100 mm/hr (IQR 60 to 103.5) to 6 mm/hr (IQR 4.5 to 7.5) at follow-up. No statistical measures were reported. **(VERY LOW)** Change in SAA levels[23] **After median 74 months follow-up:**

[20] Elevated CRP levels were not further defined, but laboratory ranges were reported to vary at each centre.
[21] Data were only available in four patients before treatment with etanercept, but were available for all five patients after treatment.
[22] Elevated ESR levels were not further defined, but laboratory ranges were reported to vary at each centre.
[23] The authors did not provide a definition for SAA, but it has been presumed to be serum amyloid A.

Outcome	Evidence statement
	• One retrospective case series (Cooray et al 2021) (n=3) reported SAA levels in 3 patients with DADA2 after initiation of etanercept: median 10.1 mg/L (IQR 8.6 to 11.3). These values were indicated to be within the normal range although normal ranges were not specified. SAA levels at baseline were not assessed or were missing and no statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence relating to acute phase reactants in patients with DAD2 after treatment with etanercept compared to baseline. Four retrospective case series reported that median CRP and ESR levels improved in patients with DADA2 after initiation of etanercept, but where normal ranges were reported, these differed within and/or across studies. One of these case series reported SAA levels in patients with DADA2 but only after initiation of etanercept (SAA levels were not available at baseline). Follow-up durations were at 3 months, after median time on etanercept of one year, at median 20.2 months after diagnosis of DADA2 and after median 74 months follow-up.**
Safety	
Safety outcomes **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. Four retrospective case series provided non-comparative evidence relating to safety in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[1]. Follow-up durations were at 3 months after starting etanercept, at median 3.5 years to after 74 months, or at median time on etanercept treatment of one year. Safety **At 3 months after starting etanercept:** One retrospective case series (Tanatar et al 2020) (n=5) reported that *"none of the patients suffered from recurrent infections and required intravenous immunoglobulin (IVIG) treatment"*. No further details were provided and statistical measures were not reported. (**VERY LOW**) Adverse events **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that no adverse reactions were reported in patients with DADA2 after initiation of etanercept. **(VERY LOW)** Number of deaths **At median time on etanercept treatment of one year:**

Outcome	Evidence statement
	• One retrospective case series (Deuitch et al 2022) (n=9[24]) reported that 1 patient died after commencing treatment with etanercept due to complications of liver disease. No further details were provided. **(VERY LOW)** **At median 3.5 years follow-up:** • One retrospective case series (Kasap Cuceoglu et al 2021) (n=18) reported that 1 patient died due to pulmonary haemorrhage.[25] No statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence on safety. Two retrospective case series reported that there were no adverse events observed in patients with DADA2 after initiation of etanercept compared to baseline, but details were limited and narratively described. Two retrospective case series each reported one death in a patient with DADA2 after initiation of etanercept but neither appeared to be directly related to etanercept treatment. Follow-up durations were at 3 months after starting etanercept, at median 3.5 years to after 74 months, or at median time on etanercept treatment of one year.**
Abbreviations ADA2: adenosine deaminase type 2 gene; APR: acute phase reactants; CNS: central nervous system; CRP: C-reactive protein; DADA2: Deficiency of adenosine deaminase type 2; ESR: erythrocyte sedimentation rate; IQR: interquartile range; IVIG: intravenous immunoglobulin; mg/L: milligrams per litre; mm/hr: millimetre per hour; MRI: magnetic resonance imaging; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amyloid A; TNF: Tumour necrosis factor.	

In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of etanercept compared with standard care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from etanercept more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that may benefit from etanercept more than the wider population of interest.

From the evidence selected, what dose of etanercept was used?

Outcome	Evidence statement

[24] Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients.
[25] , It was unclear what the sequence of events was as to when patients relapsed, when they were in remission and when the patient died as no further details were reported.

Dose of etanercept	Evidence about dose of etanercept, which is delivered via subcutaneous injection and allows patients to self-administer at home, was reported in two retrospective case series. • One retrospective case series (Cooray et al 2021) (n=5) reported etanercept doses of: 400 µg/kg twice weekly, or 800 µg/kg weekly, or 25 mg twice weekly or 50 mg weekly if >12 years old. The number of patients receiving each dose was not stated. Other treatments received after etanercept treatment included glucocorticoid and aspirin (one patient) and azathioprine (one patient). Three patients did not receive any other treatments after initiation of etanercept. • One retrospective case series (Tanatar et al 2020) (n=5) reported that four patients received 25 mg subcutaneously per week and one patient received 50 mg subcutaneously per week. One patient received concomitant fresh frozen plasma for six months. No concomitant treatments were described for the remaining patients. Etanercept doses were not reported in the seven remaining retrospective case series (Andriessen et al 2023, Celikel et al 2023, Deuitch et al 2022, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Li et al 2023, Melo et al 2023). **Two retrospective case series reported that patients with DADA2 were provided with varying doses of etanercept, ranging from 400µg/kg twice weekly to 50 mg weekly. Seven retrospective case series did not report the dose of etanercept used in the studies.**
Abbreviations DADA2: Deficiency of adenosine deaminase type 2; kg: kilogram; mg: milligram; µg: microgram.	

Adalimumab monotherapy for deficiency of adenosine deaminase 2 (DADA2)

In patients with deficiency of adenosine deaminase type 2 what is the clinical effectiveness and safety of adalimumab compared with standard care?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Number of ischaemic events **Certainty of evidence:** Very low	This is an important outcome to patients as ischaemic events are a detrimental effect of DADA2 and prevention of ischaemic events is an indication of successful treatment. Four retrospective case series provided non-comparative evidence relating to ischaemic events in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported the number of patients with ischaemic events (including stroke) at a median of 20.2 months, 36 months or between 2 and >10 years follow-up. One case series reported central nervous system (CNS)

Outcome	Evidence statement
	and non-CNS ischaemic events at a median of 12 months treatment. All outcomes are compared to baseline.[26] **Between two months and >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=9) reported that two patients, one with a history of stroke, *"developed gait disorder, diplopia and dysarthria while on TNF-inhibition [adalimumab] without abnormalities on MRI"*. None of the other patients providing data had evidence of ischaemic events before adalimumab or after initiation of adalimumab; no tests of statistical significance were performed. **(VERY LOW)** **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, 11 patients (79%) had a total of 24 ischaemic events.[27] During the follow-up period, following initiation of adalimumab, two patients reported two total ischaemic events. No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, five patients (36%) had a total of 13 CNS ischaemic events. During the follow-up period, following initiation of adalimumab, one patient reported one CNS ischaemic event. No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, seven (50%) patients had a total of 11 non-CNS ischaemic events. During the follow-up period, following initiation of adalimumab, one patient reported one non-CNS ischaemic event. No statistical tests were performed. **(VERY LOW)** **At median 20.2 months follow-up (range 23 to 48 months):** • One retrospective case series (Li et al 2023) (n=9) reported that *"… no patients have had a stroke during the time they have been on treatment".* No further details were provided, and no summary statistics were performed. **(VERY LOW)** **At median 36 months follow-up (range 23 to 48 months):** • One retrospective case series (Nihira et al 2021) (n=3) reported that "*no patient[s] had a cerebral infarction or haemorrhage after starting treatment".* No further details were

[26] Baseline was any period before the initiation of adalimumab. Treatments received before the initiation of adalimumab varied widely between studies.

[27] This outcome included both CNS and non-CNS (arteries supplying viscera and peripheries) ischaemic events. Ischaemic events were diagnosed based on clinical features together with brain MRI/MRA and/or other imaging modalities such as ultrasound scan, CT-angiography or selective visceral catheter arteriography where indicted.

Outcome	Evidence statement
	provided, and no summary statistics were performed. **(VERY LOW)** **Three retrospective case series provided very low certainty evidence of fewer ischaemic events, including strokes, following initiation of treatment with adalimumab in patients with DADA2 at median of 12, 20 and 36 months, 36 months follow-up/ outcome measurement. One retrospective case series provided very low certainty evidence that two patients had recurrent ischaemic event symptoms without MRI abnormalities following initiation of treatment with adalimumab, one of whom had had a history of stroke before treatment with adalimumab. No other patients in the series reported ischaemic events before or after treatment at between 2 months and more than 10 years follow-up. Statistical significance was not reported for any of the studies.**
Disease activity/response **Certainty of evidence:** Very low	This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of DADA2, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression. Six retrospective case series provided non-comparative evidence relating to disease activity/response in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported the disease response at a median of 20 months, 20.2 months, 36 months follow-up; median 12 months or 17 months of adalimumab treatment; or between 2 and >10 years follow-up . Disease activity/response was measured differently in each study, but all studies that used a *composite* variable or haematological measures to evaluate response to treatment are included here. All outcomes are compared to baseline. **At 2 months to >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=8) reported that more patients had anaemia following treatment with adalimumab (before adalimumab, 2/8 (25%); after initiation of adalimumab, 3/8 (38%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had thrombocytopenia following treatment with adalimumab (before adalimumab, 1/8 (13%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that neutropenia was not resolved with adalimumab treatment (before adalimumab, 3/8 (38%); after initiation of adalimumab, 3/8 (38%); neutropenia persisted in the same three patients). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that lymphopenia was not resolved with adalimumab treatment (before adalimumab, 2/8 (25%); after initiation of

Outcome	Evidence statement
	adalimumab, 2/8 (25%); lymphopenia persisted in the same two patients). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that hypogammaglobulinemia was not resolved with adalimumab treatment (before adalimumab, 1/8 (13%); after initiation of adalimumab, 1/8 (13%); hypogammaglobulinemia persisted in the same patient). **(VERY LOW)** **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported that prior to adalimumab treatment, median Paediatric Vasculitis Activity Scores (PVAS)[28] were 17.5 (IQR 13.5 to 31.3). After a median of 12 months following initiation of adalimumab treatment, median PVAS reduced (improved) to 2.0 (IQR 1.0 to 4.0). **(VERY LOW)** **At median 20 months follow-up (range 12 to 24 months):** • One retrospective case series (Melo et al 2023) reported that 100% of patients (4/4) achieved complete remission[29] following initiation of treatment with adalimumab. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported that the majority of patients were in complete remission[30] (CR: 7, 78%; PR: 2, 22%; NR: 0, 0%) after initiation of adalimumab treatment when compared to baseline (CR: 0, 0%; PR: 3, 33%; NR: 6, 67%). No statistical tests were performed. **(VERY LOW)** **At median 36 months follow-up (range 23 to 48 months):** • One retrospective case series (Nihira et al 2021) reported that 100% of patients (3/3) achieved complete response following initiation of treatment with adalimumab. No further details were provided, and no summary statistics were performed. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence of reduced <u>DADA2 disease activity</u> following initiation of treatment with adalimumab at median follow-up/ treatment**

[28] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across nine organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit.

[29] Complete remission: clinical (the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation) AND laboratory (normalisation of CRP levels in local laboratory) control achieved; Partial remission: clinical OR laboratory control achieved; Absent remission: Neither clinical nor laboratory control achieved

[30] Complete remission (CR): persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment; Partial remission (PR): good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage; No remission (NR): little or absent response with persistence of systemic flares and/or complications

Outcome	Evidence statement
	times of 20 and 36 months or between two months and greater than ten years of follow-up. One retrospective case series provided very low certainty evidence of reduced clinical vasculitic disease activity after a median of 12 months following adalimumab treatment initiation in patients with DADA2. One retrospective case series provided very low certainty evidence that neutropenia, lymphopenia and hypogammaglobulinemia were not resolved by adalimumab in patients with DADA2, but one patient no longer had thrombocytopenia. Statistical significance was not reported for any of the studies.
Symptom alleviation **Certainty of evidence:** Very low	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. Two retrospective case series provided non-comparative evidence relating to symptom alleviation in patients with DADA2 after initiation of treatment with adalimumab. One retrospective case series reported symptom alleviation at follow-up in the range of 2 months to >10 years, whilst the other case series reported outcomes following a median of 17 months of treatment. All outcomes are compared to baseline. **At 2 months to >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had cutaneous symptoms following treatment with adalimumab (before adalimumab, 6/8 (75%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had fever following treatment with adalimumab (before adalimumab, 4/8 (50%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had PAN-like rash and other cutaneous vasculitis's following treatment with adalimumab (before adalimumab, 2/8 (25%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had arthralgia following treatment with adalimumab (before adalimumab, 3/8 (38%); after initiation of adalimumab, 1/8 (13%). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had symptoms of inflammatory-bowel like (IBD-like) disease following treatment with adalimumab (before adalimumab, 1/8 (13%); after initiation of adalimumab 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had symptoms of aphthous stomatitis following treatment with adalimumab (before

Outcome	Evidence statement
	adalimumab, 4/8 (50%); after initiation of adalimumab, 1/8 (13%)). **(VERY LOW)** **At median 17 months treatment (range 4 to 60 months):** • One retrospective case series (Deuitch et al 2022) (n=7) reported that livedo was noted in one patient prior to adalimumab. Following initiation of adalimumab, clinicians noted the patient was *"clinically well, some livedo"*[31]. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported that one patient had arthritis, livedo and racemosa symptoms prior to treatment; after initiation of adalimumab the livedo and racemosa resolved and the arthritis was downgraded to *"mild joint pain".* **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported follow-up symptoms for three patients with no baseline data. After initiation of adalimumab, one patient was *"clinically well",* one patient was *"clinically well with come neutropenia"* and one patient was reporting the symptoms of seizures and paralysis. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported follow-up symptoms for two patients reported to be *"not in flare"*[32] at baseline. After initiation of adalimumab, one patient was *"clinically well"* and one patient had concurrent gastroenteritis. **(VERY LOW)** **Two retrospective case series provided very low certainty evidence of an improvement in some DADA2 symptoms following initiation of treatment with adalimumab: <u>cutaneous symptoms, fever, PAN-like rash, arthralgia, IBD-like disease, aphthous stomatitis and livedo</u>. The studies provided very low certainty evidence that more patients with DADA2 had <u>seizures/paralysis</u> on treatment with adalimumab. Numbers were small and statistical tests of significance were not reported.**
Important outcomes	
Steroid use reduction **Certainty of evidence:** Very low	This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders. Three retrospective case series provided non-comparative evidence relating to steroid use reduction in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported steroid use reduction at a median of 12, 17 and 20.2 months follow-up /treatment. All outcomes are compared to baseline.

[31] Definition of "*clinically well*" was not provided by authors
[32] Definition of *"not in flare"* was not provided by authors

Outcome	Evidence statement
	At median 12 months treatment (range 0 to 59 months): • One retrospective case series (Cooray et al 2021) (n=14) reported fewer patients were taking steroids after initiating adalimumab treatment (before adalimumab treatment: n=10 (71.4%), after initiation of adalimumab treatment: one patient remained on steroids (7.1%) and *"one patient is being weaned off steroids"*). No statistical comparisons were reported. **(VERY LOW)** **At median 17 months treatment (4 to 60 months):** • One retrospective case series (Deuitch et al 2022) (n=7) reported that fewer patients were taking steroids (prednisone) after commencing adalimumab treatment (before adalimumab: n=2 (28.6%), after initiation of adalimumab: n=1 (14.3%)). No statistical comparisons were reported. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) (n=9) reported that fewer patients were taking glucocorticoids after commencing adalimumab treatment (before adalimumab: n=9 (100%), after initiation of adalimumab: n=4 (44%)). No statistical comparisons were reported. **(VERY LOW)** **Three retrospective case series provided very low certainty evidence of steroid use reduction following initiation of treatment with adalimumab in patients with DADA2 at a median of 12, 17 and 20.2 months follow-up /treatment; no statistical comparisons were reported.**
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** Not applicable	This outcome is important for patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making. **No evidence was identified for this outcome.**
Change in acute phase reactants **Certainty of evidence:**	This outcome is important to patients as normalisation of acute phase reactants is associated with a reduction in symptoms and improved quality of life for patients. This is particularly important in children as normalisation of acute phase reactants in linked to improvements in growth.

Outcome	Evidence statement
Very low	Three retrospective case series provided non-comparative evidence relating to changes acute phase reactants (SAA, CRP and ESR) in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported changes in acute phase reactants at 12, 17 and 20.2 months follow-up /treatment. All outcomes are compared to baseline. <u>C-reactive protein (CRP)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a reduction in median CRP after initiation of adalimumab treatment (Before: n=14; 21 mg/L (IQR 11 to 125 mg/L); After: n=13; 5 mg/L (IQR 4 to 5 mg/L)[33]). **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, 10/14 patients (71.4%) reported CRP levels outside of normal range[34]; following initiation of adalimumab treatment, 1/13 patients (7.7%) had CRP levels outside of normal range. **(VERY LOW)** **At median 17 months treatment (range 4 to 60 months):** • One retrospective case series (Deuitch et al 2022) reported a reduction in median CRP after initiation of adalimumab treatment (Before: n=4; 9.7 mg/L (IQR 9.2 to 16.7 mg/L); After: n=7; 8.0 mg/L (IQR 1.6 to 8.3 mg/L)). **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported that the median CRP levels had decreased following initiation of treatment with adalimumab (Before: n=9; 40 mg/L (IQR 33 to 49 mg/L); After adalimumab:[35] 8 mg/L (IQR 8 to 8 mg/L)). No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Li et al 2023) (n=9) reported that all nine (100%) patients had elevated CRP levels before adalimumab. Following initiation of adalimumab, two patients (22.2%) had elevated CRP levels. No statistical tests were performed. **(VERY LOW)** <u>Erythrocyte sedimentation rate (ESR)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a reduction in median ESR after initiation of adalimumab treatment (Before (n=14): 52 mm/hr (IQR 29 to 104 mm/hr); After (n=13): 9 mm/hr (IQR 5 to 14 mm/hr)). **(VERY LOW)**

[33] Some patients CRP levels were indicated as being <5 (too low to measure) following adalimumab treatment; for statistical summary the level of 5 mg/L was used

[34] CRP levels >10 mg/L were indicated as being out of target range

[35] Some patients had CRP levels below detectable levels (<8 mg/L). These were coded as 8 mg/L to calculate median and IQR

Outcome	Evidence statement
	• One retrospective case series (Cooray et al 2021) reported that prior to adalimumab treatment, 10/14 DADA2 patients (71.4%) reported ESR levels outside of normal range[36]; following initiation of adalimumab treatment, one patient (7.7%) had ESR levels outside of normal range. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported median ESR levels had decreased following initiation of treatment with adalimumab (Before: n=9; 44 mm/hr (IQR 22 to 49 mm/hr); After: n=9; 8 mm/hr (IQR 8 to 8 mm/hr)). No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Li et al 2023) reported that 5/9 (55.6%) patients had elevated ESR levels before adalimumab. Following initiation of adalimumab, all patients had ESR levels within the reference range. No statistical tests were performed. **(VERY LOW)** <u>Serum amylase A (SAA)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a beneficial reduction in median serum amylase A after initiation of adalimumab treatment (Before: n=10, 85.0 mg/L (IQR 17.2 to 96.0 mg/L); After: n=7, 7.0 mg/L (IQR 4.8 to 12.2 mg/L)). **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=10) reported that prior to adalimumab treatment, seven patients (70%) reported serum amylase A levels outside of normal range; following initiation of adalimumab treatment, no patients (0%) had SAA levels outside of normal range (normal ranges were not specified). **(VERY LOW)** **Three retrospective case series provided very low certainty evidence that median <u>CRP and ESR levels</u> improved in patients with DADA2 after initiation of treatment with adalimumab. One case series provided very low certainty evidence of an improvement in <u>serum amylase A levels</u> in patients with DADA2 following initiation treatment with adalimumab, with all patients having levels within the normal range when on treatment. Follow-up durations ranged from 2 months to >10 years; no statistical measures were reported.**
Safety	
Safety outcomes **Certainty of evidence:**	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective,

[36] CRP levels >10 mg/L were indicated as being out of target range

Outcome	Evidence statement
Very low	they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. Two retrospective case series provided non-comparative evidence relating to safety in patients with DADA2 after initiation of treatment with adalimumab. One retrospective case series reported the disease response at a median of 20.2 months follow-up and the other at a median of 12 months of treatment. <u>Adverse Events</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) stated that *"no adverse events were reported with adalimumab or etanercept"* following a median of 12 months of treatment. **(VERY LOW)** <u>Deaths</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported that one patient had bone marrow failure and died of complications of sepsis and bowel perforation; the patient had one dose of adalimumab. **(VERY LOW)** **At median 20 months follow-up (range 12 to 24 months):** • One retrospective case series (Melo et al) reported that one patient, treated with adalimumab, died during the follow-up period due to disseminated staphylococcal infection. **(VERY LOW)** **One retrospective case series provided very low certainty evidence that no <u>adverse events</u> were observed following treatment with adalimumab in patients with DADA2; details were limited. Two retrospective case series provided very low certainty evidence that two patients died during the follow-up period, but there was no evidence that these <u>deaths</u> related to adalimumab therapy. Median follow-up was less than 24 months for safety reporting.**

Abbreviations

CNS: central nervous system; CR: complete remission; CRP: C reactive protein; CT: computerised tomography; DADA2: Deficiency of Adenosine Deaminase-2; ESR: erythrocyte sedimentation rate; hr: hour; IBD: Inflammatory bowel disease; IQR: interquartile range; n: number; L: litre; mg: milligrams; mm: millimetres; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; NR: no remission; PAN: polyarteritis nodosa; PR: partial remission; Pt: patient; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amylase A; TNF: Tumour Necrosis Factor

From the evidence selected, are there any subgroups of patients that may benefit from adalimumab more than the wider population of interest?

Outcome	Evidence statement

Subgroups	No evidence was identified regarding any subgroups of patients that may benefit from adalimumab more than the wider population of interest.

In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of adalimumab compared with standard care?

Outcome	**Evidence statement**
Cost effectiveness	No evidence was identified for cost effectiveness.

Patient Impact Summary

If untreated, Deficiency of Adenosine Deaminase 2 (DADA2) can lead to both childhood and adult strokes which have the following impacts on the patient's everyday life:

- **mobility:** Patients have severe problems in walking about OR are unable to walk about.
- **ability to provide self-care:** Patients have severe problems in washing or dressing OR are unable to wash or dress.
- **undertaking usual activities:** Patients have severe problems in doing their usual activities OR are unable to do their daily activities.
- **experience of pain/discomfort:** Patients have moderate to severe pain or discomfort.
- **experience of anxiety/depression:** Patients are extremely anxious or depressed.

Further details of impact upon patients:

DADA2 can cause a multitude of symptoms and problems for patients. Strokes and its sequalae are a major issue and burden that patients with DAD2 face, especially when the age of onset of strokes is so young.

Strokes in early childhood can lead to delayed motor, language, emotional, social, and cognitive development, with lifelong consequences. Adults then experience lower rates of employment and productivity and may struggle with their mental wellbeing as a direct result.

DADA2 can also lead to patients being immunocompromised and therefore at much higher risk of recurrent infections. Patients may spend a long time recovering from infections, only to be re-infected. All of these complications of DADA2 can lead to long-term organ damage and increased morbidity.

Further details of impact upon carers:

Parents and caregivers may struggle to come to terms with the diagnosis, and may experience a range of emotions including anger, fear, anxiety, and stress. Caring for a child or adult following a stroke caused by DADA2 may be associated with an enhanced need for caring support throughout the patient's whole life, special schooling requirements, and significant financial impacts for the household.

Considerations from review by Rare Disease Advisory Group
• Members supported the policy of enabling access for this in-year service development; • Members supported early diagnosis so that patients could benefit as early as possible; • Members suggested that patients should be started on the drug as early as possible to (hopefully) avoid consequences of the condition; • Members requested consideration of the potential for national data collection; • Members queried the relationship between anti-TNF inhibitors and bone marrow transplant and how this might play out in the longer-term particularly for the youngest patient cohort. The Clinical Fellow confirmed that BMT is indicated for a small subgroup of DADA2 patients who have severe bone marrow failure: this subgroup do not respond well to anti-TNF therapies.

Pharmaceutical considerations
This clinical commissioning policy proposition is for the use of etanercept and adalimumab for the treatment of deficiency of adenosine deaminase type 2 in people aged 5 years and older. The recommendations are outside of the marketing authorisations for etanercept and adalimumab, so use is off-label and Trust policy regarding unlicensed medicines should apply. Both etanercept and adalimumab are on the NHS Payment Scheme Annex A, that is, they are high-cost drugs. The policy proposition covers use in people aged 5 years and over, in line with the findings from the evidence review. Etanercept and adalimumab may be used in children aged 2 – 5 years by application of the NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children),as both drugs are listed in the BNF Children with a recommended dosage schedule relative to the age of the child.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection PoC on the 22 October 2024.