Additional file 4. Exploratory synthesis: mycophenolate mofetil versus no mycophenolate, ≥50% rise in serum creatinine

A post hoc exploratory synthesis. It was carried out because the two trials answer a shared treatment question, and the assessment of that question is set out in Additional file 12, section 2.1. The calculation is reported transparently, with the differences between the trials stated, and it is **not** part of the clinical synthesis: no treatment conclusion of this review rests on it.

1. Studies, counts and intervals

Item	Value
Trials	Frisch 2005 (double-blind; MMF titrated up to 1000 mg twice daily for one year against identical placebo; the primary outcome was a **sustained** 50% rise in serum creatinine from baseline observed for at least two consecutive months; achieved mean total follow-up 59 weeks in the MMF arm and 75 weeks in the placebo arm): 5/17 versus 2/15. Tang 2005 (MMF 1.5–2 g/day for 24 weeks added to ongoing treatment, versus continuation of that treatment; not placebo-controlled; 72 weeks of follow-up; no persistence requirement stated for the creatinine rise): 1/20 versus 3/20
Participants and events	72 patients; 11 events
Study odds ratios (calculated from the counts)	Frisch 2.71 (0.44 to 16.68); Tang 0.30 (0.03 to 3.15)
Fixed-effect OR	1.19 (0.28 to 5.01)
Random-effects OR (DerSimonian–Laird, normal interval)	1.03 (0.12 to 8.78)
Hartung–Knapp–Sidik–Jonkman interval	9.3×10^{-7} to 1.1×10^{6}
Heterogeneity	$I^2 = 52.6\%$; $Q = 2.112$, $df = 1$, $P = 0.146$
Leave-one-out	Omitting either trial leaves a single study

2. Why the result is exploratory

The two trials differ in the confirmation requirement for the creatinine rise (at least two consecutive months versus none stated), in the control condition (double-blind placebo versus open continuation of ongoing treatment), in the entry criteria (creatinine clearance 20–80 mL/min with a mean baseline serum creatinine of 2.4 mg/dL, versus persistent proteinuria with serum creatinine below 3.4 mg/dL) and in the achieved follow-up. Frisch has no retrievable registration record and Tang does not describe the randomisation method. These differences do not forbid the calculation — they are the reason its result is reported as exploratory and is not carried into the clinical synthesis.

3. What the intervals do and do not show

With two studies the pooled interval is highly sensitive to the method of inference. Where the DerSimonian–Laird estimate of τ^2 is greater than zero, the Hartung–Knapp–Sidik–Jonkman

standard error equals the DerSimonian–Laird standard error at k = 2 and only the critical value differs (t = 12.706 versus 1.96); where τ^2 is truncated to zero, the Hartung–Knapp–Sidik–Jonkman interval can be markedly narrower. The three intervals are therefore reported side by side.

The conclusion drawn is **not** that a two-study synthesis is inadmissible, and **not** that the interval reflects the method rather than the data: the data fix the estimate and the between-study variance, and the method determines how that variance is propagated into an interval. The conclusion is narrower. With k = 2, I^2 = 52.6% and the two trial estimates pointing in opposite directions, the pooled interval is compatible with appreciable benefit and with appreciable harm, so it does not distinguish between them. This behaviour is a property of k = 2 with these data; it is not a general statement that every two-study interval is unreliable.