Appendix 1 Glucocorticoid (prednisolone or equivalent) dose regimen in key trials: PEXIVAS versus other 9 trials
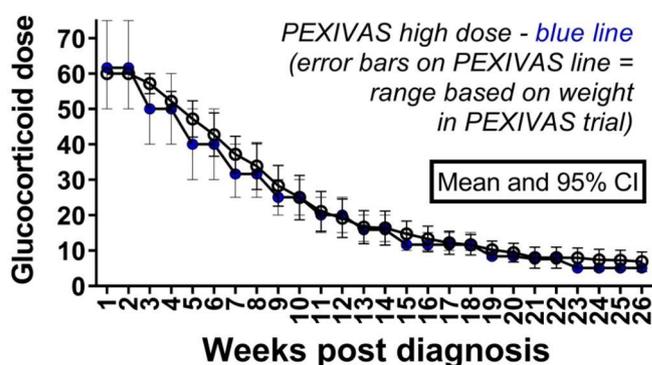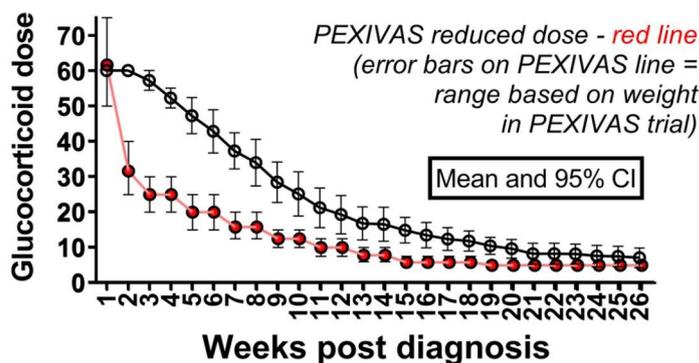

Figure legend : The other 9 trials include :
1.   Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.
2.   De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9.
3.   Stassen PM, Tervaert JWC, Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. Ann Rheum Dis 2007;66:798–802.
4.   Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 2007;57:686–93.
5.   ayne DRW, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180–8.
6.   de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.
7.   Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.
8.   Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
9.   Mansfield N, Hamour S, Habib AM, et al. Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. Nephrol Dial Transplant 2011;26:3280–6.

Appendix 2 First panel survey of values and preferences towards plasma exchange in patients with ANCA-associated vasculitis (AAV)

Before the first panel meeting, 21 panel members completed an online survey asking them to, based on their experience, hypothesize the magnitude of reduction in end-stage kidney disease that, given its associated increase in serious infections, patients would require to choose plasma exchange. To minimize the influence of preconceived beliefs regarding the advisability of using plasma exchange, we did not present, prior to or in the survey, the estimated effect of plasma exchange in reduction of end-stage kidney disease.

One patient and one caregiver completed the questionnaire together, so we received 20 responses in total. The panel members stopped answering questions when they moved from "majority would decline plasma exchange" to "majority would choose plasma exchange" (i.e. they identified the threshold for benefit). Therefore, the total number of votes for individual questions sometimes less than 20. The following presents the survey questionnaire followed by panel members' votes. Finally, we summarize the thresholds identified by individual panel members.

Introduction
Plasma exchange may reduce the risk of some outcomes, such as end-stage kidney disease but at the cost of an increased risk of adverse events. We need to understand what degree of benefit (in terms of a reduced risk of end-stage kidney disease) would be required to accept the risks of adverse events. Below we will provide information on the potential risks of plasma exchange. You will then be presented with a series of questions asking if you believe patients would choose to receive plasma exchange under a specific scenario in terms of reducing end-stage kidney disease but increasing in the risk of serious infection. Each question will vary the risk reduction of end-stage kidney disease and the risk increase of serious infection. Please read these carefully.

"Values and preferences regarding plasma exchange for adults with ANCA-associated vasculitis and kidney involvement and/or diffuse pulmonary hemorrhage differ markedly. Some patients might choose to receive plasma exchange with a very small benefit on the absolute risk reduction of end-stage kidney disease, and some will be reluctant to take it even if there is a large benefit."
Would you agree or disagree with this statement?*
- Agree: 16
- Disagree: 4

Here we give a summary of the harms, burdens and benefits other than risk reduction on end-stage kidney disease of plasma exchange that you should bear in mind when you answer the follow questions.
Harms and burdens:
- Plasma exchange increased the risk of serious infection (defined as requiring hospitalization or intravenous antibiotics) compared with usual care in the first year. The absolute risk increase is 6 more per 100 patients.
- Plasma exchange may result in the transmission of serious viral infections such as hepatitis B, hepatitis C or HIV in less than 1 in 7 million patients.
- Plasma exchange results in transfusion related acute lung injury in about 1 in 12,000 patients.
- Plasma exchange is performed several times during a period of approximate 2 weeks.
- Some patients receiving plasma exchange need central line placement.

Benefits other than risk reduction on end-stage kidney disease:
- Plasma exchange did not affect death or disease relapse at 12 months or after longer follow-up.

In the first year, a patient who takes plasma exchange has a **1 in 100 (1%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?

- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 3
- Majority (51-74%) would **choose** plasma exchange: 2
- Majority (51-74%) would **decline** plasma exchange: 5
- Most (75-90%) would **decline** plasma exchange: 4
- All or almost all (over 90%) would **decline** plasma exchange: 6

In the first year, a patient who takes plasma exchange, has a **15 in 100 (15%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?

- All or almost all (over 90%) would **choose** plasma exchange: 6
- Most (75- 90%) would **choose** plasma exchange: 5
- Majority (51-74%) would **choose** plasma exchange: 2
- Majority (51-74%) would **decline** plasma exchange: 2
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **2 in 100 (2%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?

- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 0
- Majority (51-74%) would **choose** plasma exchange: 0
- Majority (51-74%) would **decline** plasma exchange: 4
- Most (75-90%) would **decline** plasma exchange: 6
- All or almost all (over 90%) would **decline** plasma exchange: 3

In the first year, a patient who takes plasma exchange, has a **14 in 100 (14%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?

- All or almost all (over 90%) would **choose** plasma exchange: 6
- Most (75- 90%) would **choose** plasma exchange: 3
- Majority (51-74%) would **choose** plasma exchange: 4
- Majority (51-74%) would **decline** plasma exchange: 0
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **3 in 100 (3%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?

- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 1
- Majority (51-74%) would **choose** plasma exchange: 2
- Majority (51-74%) would **decline** plasma exchange: 3
- Most (75-90%) would **decline** plasma exchange: 7

- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **13 in 100 (13%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 5
- Most (75- 90%) would **choose** plasma exchange: 2
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 0
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **4 in 100 (4%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 0
- Majority (51-74%) would **choose** plasma exchange: 2
- Majority (51-74%) would **decline** plasma exchange: 4
- Most (75-90%) would **decline** plasma exchange: 4
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **12 in 100 (12%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 2
- Most (75- 90%) would **choose** plasma exchange: 3
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 0
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **5 in 100 (5%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 1
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 2
- Most (75-90%) would **decline** plasma exchange: 2
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **11 in 100 (11%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 1
- Majority (51-74%) would **choose** plasma exchange: 4
- Majority (51-74%) would **decline** plasma exchange: 0
- Most (75-90%) would **decline** plasma exchange: 0

- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **6 in 100 (6%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 0
- Majority (51-74%) would **choose** plasma exchange: 0
- Majority (51-74%) would **decline** plasma exchange: 4
- Most (75-90%) would **decline** plasma exchange: 1
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **10 in 100 (10%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 1
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 1
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **7 in 100 (7%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 0
- Majority (51-74%) would **choose** plasma exchange: 1
- Majority (51-74%) would **decline** plasma exchange: 3
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **9 in 100 (9%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 0
- Majority (51-74%) would **choose** plasma exchange: 0
- Majority (51-74%) would **decline** plasma exchange: 3
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **8 in 100 (8%) lower risk of end-stage kidney disease** and a **6 in 100 (6%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 0
- The majority would **decline** plasma exchange: 0
- Most would **decline** plasma exchange: 0

- All or almost all would **decline** plasma exchange: 0

Now consider that the risk of serious infection is 18% instead of 6% and other burdens and harms were the same. Now, what would patients choose.

In the first year, a patient who takes plasma exchange, has a **1 in 100 (1%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 3
- The majority would **decline** plasma exchange: 3
- Most would **decline** plasma exchange: 4
- All or almost all would **decline** plasma exchange: 10

In the first year, a patient who takes plasma exchange, has a **15 in 100 (15%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 4
- Most would **choose** plasma exchange: 5
- The majority would **choose** plasma exchange: 3
- The majority would **decline** plasma exchange: 3
- Most would **decline** plasma exchange: 2
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **2 in 100 (2%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 1
- The majority would **decline** plasma exchange: 3
- Most would **decline** plasma exchange: 3
- All or almost all would **decline** plasma exchange: 5

In the first year, a patient who takes plasma exchange, has a **14 in 100 (14%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 2
- Most would **choose** plasma exchange: 6
- The majority would **choose** plasma exchange: 3
- The majority would **decline** plasma exchange: 0
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **3 in 100 (3%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0

- The majority would **choose** plasma exchange: 1
- The majority would **decline** plasma exchange: 3
- Most would **decline** plasma exchange: 4
- All or almost all would **decline** plasma exchange: 3

In the first year, a patient who takes plasma exchange, has a **13 in 100 (13%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 2
- Most would **choose** plasma exchange: 6
- The majority would **choose** plasma exchange: 1
- The majority would **decline** plasma exchange: 1
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **4 in 100 (4%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 0
- The majority would **decline** plasma exchange: 4
- Most would **decline** plasma exchange: 4
- All or almost all would **decline** plasma exchange: 1

In the first year, a patient who takes plasma exchange, has a **12 in 100 (12%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 7
- The majority would **choose** plasma exchange: 2
- The majority would **decline** plasma exchange: 0
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **5 in 100 (5%) lower risk of end-stage kidney disease** and **an 18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 1
- The majority would **decline** plasma exchange: 5
- Most would **decline** plasma exchange: 3
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **11 in 100 (11%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 5

- The majority would **choose** plasma exchange: 3
- The majority would **decline** plasma exchange: 0
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **6 in 100 (6%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 2
- The majority would **decline** plasma exchange: 6
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **10 in 100 (10%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 4
- The majority would **choose** plasma exchange: 2
- The majority would **decline** plasma exchange: 0
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **7 in 100 (7%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 3
- The majority would **decline** plasma exchange: 3
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **9 in 100 (9%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection** in addition to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0
- The majority would **choose** plasma exchange: 2
- The majority would **decline** plasma exchange: 1
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange: 0

In the first year, a patient who takes plasma exchange, has a **8 in 100 (8%) lower risk of end-stage kidney disease** and an **18 in 100 (18%) increased risk of serious infection in addition** to the other risks noted above. Given the harms and burdens of plasma exchange, how would patients view such benefits?
- All or almost all would **choose** plasma exchange: 0
- Most would **choose** plasma exchange: 0

- The majority would **choose** plasma exchange: 1
- The majority would **decline** plasma exchange: 1
- Most would **decline** plasma exchange: 0
- All or almost all would **decline** plasma exchange:0

Summary: **Given two levels of harm (increase in serious infections), the threshold for benefit (reduction in end-stage kidney disease) identified by individual panel members**

Panel member number	The threshold for reduction in end-stage kidney disease (expressed as the number reduced end-stage kidney disease per 100 patients)	
	6% increased risk of serious infections	18% increased risk of serious infections
#1	1	9
#2	1	1
#3	1	1
#4	1	2
#5	1	1
#6	3	15
#7	3	7
#8	3	3
#9	4	7
#10	4	5
#11	5	7
#12	5	8
#13	5	14
#14	7	10
#15	10	15
#16	10	15
#17	10	15
#18	11	6
#19	15	6
#20	15	15
Range	1-15	1-15
Median	4.5	7

Conclusions
Based on the results of the first survey, the panel acknowledged a likely large variation in patients' values and preferences regarding the trade-off between benefits (e.g. reduction in death or ESKD) and harms (e.g. increase in serious infections). The survey revealed : 1) Given a 6% increased risk of serious infections, most patients would want a benefit of at least 4.5% reduction in end-stage kidney disease in a time frame of 1 year (the median of the panel's votes) for plasma exchange; 2) if the risk increase in serious infections was 18% (instead of 6%), most patients would want a benefit of at least 7% decrease in risk of end-stage kidney disease (the median of the panel's votes) for plasma exchange. The panel concluded that patients put a higher value on end-stage kidney disease and a relative less value on serious infections.

Appendix 3 Second panel survey of values and preferences towards plasma exchange in patients with ANCA-associated vasculitis (AAV)

The absolute effects of plasma exchange on both reduction in end-stage kidney disease and increase in serious infections increase as patients' serum creatinine rises. The second survey asked panel members, based on their own experience, to make judgements about how patients within particular ranges of serum creatinine level would view the trade-off between benefit (i.e. reduction in end-stage kidney disease) and harm (i.e. increase in serious infections) of plasma exchange. Of the 22 panel members, 19 completed the online survey. One patient and one caregiver completed the questionnaire together, so we received 18 responses in total. The survey questionnaire and panel members' votes are as follows (number of votes given after each response alternative):

Introduction

Purpose of this survey: We would like to know the panel's perspective regarding your view about the distribution of choices individuals would make after full shared decision-making regarding whether or not to use plasma exchange. We will use your responses to inform our discussion of the tipping point, with regard to baseline creatinine levels, at which the majority would switch from declining to accepting plasma exchange.

Content of this survey: We will present to you 1) a summary of your views of patients' values and preferences towards plasma exchange from the first panel survey; 2) the benefits (absolute risk reduction in end-stage kidney disease) and harms (absolute risk increase in serious infections) of plasma exchange in patients with ANCA-associated vasculitis and with baseline creatinine at <200µmol/Lµmol/L, 200-300µmol/Lµmol/L, 300-400µmol/Lµmol/L, 400-500µmol/L, >500µmol/L. We will then ask you for your perspective about what proportion of patients would choose plasma exchange under each condition.

Each question will vary the risk reduction of end-stage kidney disease and the risk increase of serious infection. Please read these carefully.

Summary of values and preferences towards plasma exchange from the first panel survey

If a patient who takes plasma exchange has a **6 in 100 increased risk of serious infection** in the first year, the panel thinks the patient would require at least a **4.5 in 100 decreased risk of end-stage kidney disease**.

If a patient who takes plasma exchange has an **18 in 100 increased risk of serious infection** in the first year, the panel thinks the patient would require at least **a 7 in 100 decreased risk of end-stage kidney disease**

Second panel survey

1. For patients with ANCA-associated vasculitis and with **serum creatinine < 200µmol/L**, how would patients view the trade-off between the benefits and harms of plasma exchange?

Benefits: **0.4 in 100 lower risk** of end-stage kidney disease at 1 year
Harms: **2.7 in 100 increased risk** of serious infections at 1 year

- All or almost all (over 90%) would **choose** plasma exchange: 0
- Most (75- 90%) would **choose** plasma exchange: 4
- Majority (51-74%) would **choose** plasma exchange: 0
- Majority (51-74%) would **decline** plasma exchange: 1
- Most (75-90%) would **decline** plasma exchange: 6
- All or almost all (over 90%) would **decline** plasma exchange: 7

2. For patients with ANCA-associated vasculitis and with **serum creatinine > 500µmol/L**,

how would patients view the trade-off between the benefits and harms of plasma exchange?

Benefits: **16.8 in 100 lower risk** of end-stage kidney disease at 1 year
Harms: **13.5 in 100 increased risk** of serious infections at 1 year
- All or almost all (over 90%) would **choose** plasma exchange: 9
- Most (75- 90%) would **choose** plasma exchange: 6
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 0
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange:0

3. For patients with ANCA-associated vasculitis and with **<u>serum creatinine 200-300μmol/L</u>**, how would patients view the trade-off between the benefits and harms of plasma exchange?

Benefits: **3.1 in 100 lower risk** of end-stage kidney disease at 1 year
Harms: **4.9 in 100 increased risk** of serious infections at 1 year

- All or almost all (over 90%) would **choose** plasma exchange: 2
- Most (75- 90%) would **choose** plasma exchange: 2
- Majority (51-74%) would **choose** plasma exchange: 3
- Majority (51-74%) would **decline** plasma exchange: 8
- Most (75-90%) would **decline** plasma exchange: 2
- All or almost all (over 90%) would **decline** plasma exchange: 1

4. For patients with ANCA-associated vasculitis and with **serum creatinine <u>400-500μmol/L</u>**, how would patients view the trade-off between the benefits and harms of plasma exchange?

Benefits: **10.4 in 100 lower risk** of end-stage kidney disease at 1 year
Harms: **9.7 in 100 increased risk** of serious infections at 1 year

- All or almost all (over 90%) would **choose** plasma exchange: 5
- Most (75- 90%) would **choose** plasma exchange: 8
- Majority (51-74%) would **choose** plasma exchange: 4
- Majority (51-74%) would **decline** plasma exchange: 1
- Most (75-90%) would **decline** plasma exchange: 0
- All or almost all (over 90%) would **decline** plasma exchange: 0

5. For patients with ANCA-associated vasculitis and with **serum creatinine <u>300-400μmol/L</u>**, how would patients view the trade-off between the benefits and harms of plasma exchange?

Benefits: **5.7 in 100 lower risk** of end-stage kidney disease at 1 year
Harms: **7.3 in 100 increased risk** of serious infections at 1 year

- All or almost all (over 90%) would **choose** plasma exchange: 3
- Most (75- 90%) would **choose** plasma exchange: 1
- Majority (51-74%) would **choose** plasma exchange: 12
- Majority (51-74%) would **decline** plasma exchange: 1
- Most (75-90%) would **decline** plasma exchange: 1
- All or almost all (over 90%) would **decline** plasma exchange: 0

Conclusions

The majority of panel members think that the majority of patients with serum creatinine < 300 µmol/L would decline plasma exchange, while the majority of patients with serum creatine ≥ 300 µmol/L would choose plasma exchange.

Appendix 4 Rapid Recommendation panel members and their declaration of interests

Clinical Chair	
Alfred Mahr Rheumatologist	Rheumatology Clinic, Department of Internal Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland
Methods Co-Chair coaches	
Gordon Guyatt General internist, guideline expert, methodologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada ; Department of Medicine, McMaster University, Hamilton, Ontario, Canada
Reed Siemieniuk General internist, General internist, guideline expert, methodologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
Methods Co-Chair	
Linan Zeng Methodologist, pharmacist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada ; Pharmacy department/Evidence-based pharmacy center, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China
Clinical Experts	
Lynn Fussner Intensivist, pulmonologist	Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA
Karin Kilian Rheumatologist	Department of Rheumatology, Oslo University Hospital, Oslo, Norway; Institute of Clincal Medicine, University of Oslo, Oslo, Norway.
Mark Little Nephrologist	Trinity Translational Medicine Institute, Trinity College Dublin, Ireland ; Irish Centre for Vascular Biology, Tallaght University Hospital, Dublin, Ireland
Thomas Mavrakanas Nephrologist	Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland ; Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada
Reem A. Mustafa Nephrologist	Department of Internal Medicine, Division of Nephrology and Hypertension, University of Kansas Medical Center, Kansas, United States
Maryam Piram Pediatrician	CHU Sainte Justine Research Center, Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada ; CEREMAIA, Centre d'épidémiologie et de santé des populations (CESP), University Paris-Saclay, Le Kremlin Bicêtre, France
Lisa Katrina Stamp Rheumatologist	University of Otago Christchurch, University of Otago, Christchurch, New Zealand

Michael Walsh Nephrologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada ; The Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada ; Department of Medicine, McMaster University, Hamilton, Ontario, Canada; St. Joseph's Healthcare, Hamilton, Ontario, Canada
Patient/Caregiver Partners	
Michelle Booth	United States
Paul Brown	United States
Mark Farrar	United Kingdom
Lesha Farrar	United Kingdom
Tracy Firth	United Kingdom
Methods Experts	
Thomas Agoritsas General internist, guideline expert, methodologist	Division of General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland ; Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
David Collister Patient liaison, nephrologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada ; The Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada ; Department of Medicine, McMaster University, Hamilton, Ontario, Canada; St. Joseph's Healthcare, Hamilton, Ontario, Canada
Lyubov Lytvyn Patient liaison, methodologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
Per O. Vandvik General internist, guideline expert, methodologist	Department of Medicine, Lovisenberg Hospital Trust, Oslo, Norway~~Department of Health Economics and Health Management, Institute for Health and Society, University of Oslo, Oslo, Norway~~
Yingqi Xiao Methodologist of systematic review	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada ; West China School of Nursing / Department of Nursing, West China Hospital, Sichuan University, China.

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the BMJ Rapid Recommendations. The pre-screening was performed by the RapidRecs steering committee, affiliated with the non-profit organisation MAGIC (www.magicproject.org) and with support and approval from at least two unconflicted BMJ editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in gastric acid suppressants) and intellectual and professional conflicts of interest were managed appropriately (see appendix 2: Methods for BMJ Rapid Recommendations). Panel members could not have a conflict for the past three years and

do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

Disclosures

<u>Financial disclosures</u>: No panel members had any financial conflicts of interest to disclose related to this clinical question.

<u>Professional disclosures</u>: Almost all of the physician panel members routinely see patients to whom this guideline applies, but their practice, rank, and remuneration will be unaffected by these recommendations.

<u>Intellectual disclosures</u>: Michael Walsh, David Collister, Gordon Guyatt, Alfred Mahr, Linan Zeng, Yingqi Xiao, and Reed Siemieniuk participated in writing the systematic review that formed the evidence base for this guideline (doi: XX). Michael Walsh participated in writing the prognostic study that support the stratification of recommendations in this guideline (doi: XX). Michael Walsh is the co-PI of PEXIVAS trial. Reed Siemieniuk, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, Linan Zeng and Gordon Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods.

Appendix 5 Methodology for development of BMJ Rapid Recommendations

About *BMJ* Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. <u>On a daily basis, we monitor the literature for practice-changing evidence:</u>
   a. Formal monitoring through McMaster Premium LiteratUre Service (PLUS)
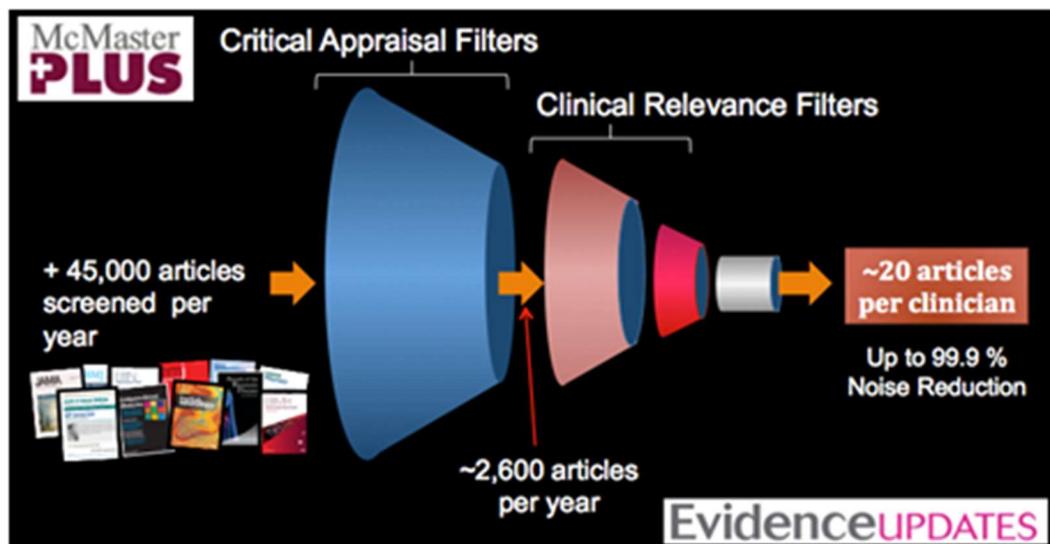
   b. Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients
2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.
3. <u>We incorporate the evidence into the existing body of evidence</u> and broader context of clinical practice via:
   a. a rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients
   b. parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.

c. The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]

d. Further research may be conducted including:

    i. A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the clinical question, a key component when calculating the estimates of absolute effects of the intervention

    ii. A systematic review on the preferences and values of patients on the topic.

4. <u>Disseminate the rapid recommendations through</u>

a. publication of the research in *BMJ* journals

b. short summary of recommendations for clinicians published in *The BMJ*

c. press release and/or marketing to media outlets and relevant parties such as patient groups

d. Links to BMJ Group's *Best Practice* point of care resource

e. MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves

a. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]

b. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process.

The following panel members are important

- At least one author of the individual systematic reviews

- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.

- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.

- Methodological experts in health research methodology and guideline development

Any potential conflicts of interest are managed with extreme prudence:

  - No panel member can have a financial interest – as assessed by the panel chair, the *Rapidrecs* executive team or *The BMJ* editors as relevant to the topic

  - No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, the panel recruitment of content experts and community panel members was challenging. Content experts in this area are infectious diseases experts, many of whom have financial conflicts of interests through interactions with the pharmaceutical industry through advisory boards and participation in industry-funded trials. The group reached out to more than 17 potential panel members who were eventually excluded from participating because of conflicts – notably, all of these persons had not disclosed any relevant conflicts on related and recent publications in the topic area. Many more potential panel members were not recruited because of publicly declared conflicts. The chair and MAGIC team were able, with considerable effort and ingenuity, to recruit several excellent and unconflicted content experts.

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.

2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.

3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to *The BMJ*. Additional teleconferences are arranged as needed.

Illustrative example: *For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, two large-group teleconferences were arranged. First, content experts provided crucial input to evidence assessment (e.g. subgroups to identify). For the recommendation formulation phase the panel needed two teleconferences to discuss all elements in detail, followed by more than 100 e-mails with specific issues to be sorted out. Multiple teleconferences were held to allow the scheduling flexibility required so that all could participate.*

How we move from research findings to recommendations

What information is considered?
The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the *BMJ* Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?
The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***
- This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available.   - We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",**

- Interests of each panel member are declared prior to involvement and published with the rapid recommendations
- No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*
- No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic.
- The Chair must have methods expertise, a clinical background and no financial or intellectual interests.
- Funders and pharmaceutical companies have no role in these recommendations.

3. Guideline Development Group Composition

"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"

- *The RapidRecs* group will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender-balance.
- We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available
- Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.

4. Clinical Practice Guideline–Systematic Review Intersection

"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".

- Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton.
- The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process

5. Establishing Evidence Foundations for and Rating Strength of Recommendations

"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation

systematic and transparent assessments are made across the following key factors:

- ○ Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
- ○ Quality of the evidence[7]
- ○ Values and preferences of patients
- ○ Resources and other considerations (e.g. feasibility, applicability, equity)

- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.[8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders....., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment.."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy
- A *BMJ* series adviser with methodological and/or statistical expertise will review the

BMJ Rapid Recommendations publication and the systematic reviews.

- The *Rapidrecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable
- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

8. Updating

"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The *Rapidrecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

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