Reviewer's report

**Title:** The GRADE approach for assessing new technologies: the case of apheresis in Ulcerative Colitis.

**Version:** 1  **Date:** 7 October 2009

**Reviewer:** Yngve T Falck-Ytter

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In their manuscript, Ibargoyen-Roteta et al. are answering an important question whether using the GRADE methodology works well in health technology assessments (HTA) by carrying out an HTA on apheresis in ulcerative colitis (UC) utilizing a previous systematic review.

**Strengths of the study:**

The authors went to great length to identify all relevant studies, critically appraised the included trials, and adequately pooled the results (when applicable) through meta-analyses. The authors then correctly applied the GRADE methodology to create GRADE evidence profiles and finally to arrive to clinical recommendation by applying critical steps of the GRADE approach. Finally, a SWOT analysis was done to appraise the GRADE process.

However, there are a few points that the authors may want to address to clarify their findings:

- **Major Compulsory Revisions**
  - Page 11 and second main recommendation on page 12: the authors state: “Therefore, this treatment could be used as the first choice in patients presenting toxicity to corticosteroids or especially in children...”. As far as I can tell, studies included neither a defined group of patients presenting with steroid toxicity nor did they included children. The stated recommendation therefore does not appear to be supported by the evidence. Please clarify.
  - Table 2: Footnote 1 states that one included trial was not randomized but rather observational in nature. The authors should clarify if mixing experimental with observational data within a meta-analysis is desirable.
  - Table 2 (and 3): Footnote 6 (and 1 in table 3): GRADE does not recommend to automatically downgrade for inconsistency just for the reason of having only one study. Consider revising.
  - Table 3: Footnote 2: After describing the limitations, the authors note that the limitations were not serious enough to warrant downgrading. However, the profile shows that the quality was downgraded one level. Please clarify.

- **Minor Essential Revisions**
  - Page 13: “Moreover, in case series, it is reported that a high percentage of
corticodependent patients are free for corticosteroids after adjunct apheresis treatment…": It is confusing to cite additional evidence (case series) which is not included in the evidence profiles. Would recommend moving to the discussion section.

- Table 4: S4: The authors state that one strength of the GRADE system is its “quantitative assessment of the quality of studies”. However, GRADE is not considered quantitative (there is no point system); rather, the quality moves from a higher to a lower level, OR from a lower level to a higher (and in most instances not down AND up again). Also, a central feature of the GRADE system is the rating of the quality of outcomes (in comparison of studies). Would therefore suggest to rephrase to: “Explicit assessment of the quality of outcomes across studies”

- Table 4: W2: Not sure what the authors mean with “Not a direct method establishing recommendations”.

- Table 4: W4: “In continued development: there is not [the word not is assumed – it is not correctly displayed in the pdf version of the manuscript] a final version yet”. Although some elements may continue to be developed (as research into methodology in general continues to evolve), the second part of this statement is not correct: the core GRADE system has been finalized and used by multiple organizations for many years.

- Table 4: T1: Threats: “Difficulties with new technologies: low number of studies, heterogeneity, unsuitable outcomes…” Not sure what the authors mean with that statement. It does not appear to refer to the GRADE methodology because the threats mentioned are inherent to the assessment of some new technologies with limited evidence base and not a reflection of GRADE or any other system that would be used to support an HTA. This applies to T3 as well. Please clarify.

- Discretionary Revisions

- Page 11: Instead of stating: “using apheresis systems instead of corticosteroids seems to have the same efficacy…” would suggest to state there were “no differences in efficacy”.

- Table 1: Some overall judgments of the importance of outcomes are not entirely intuitive. For example, if researchers R1 to R5 judge the clinical remission at 12 months to be 7, 6, 8, 6, 8 and critical is defined as 7 to 9, then it appears that this outcome should be critical. However, if the group resolved this by discussion and decided to call this “important” instead (which is the usual process), then this should be noted in a footnote.

- Table 2: Would recommend changing the heading from GRADEpro table to the suggested GRADE terminology: “GRADE evidence profile”.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no financial competing interest. I may have some intellectual competing interest in the sense that I have contributed to the development of GRADE and as such may have a positive bias towards the GRADE system.