

### **Supplementary Table 1 Rome IV diagnostic criteria for functional constipation in children**

Diagnostic criteria must include at least 2 of the following features of constipation for a minimum of 1 month, occurring at least once per week in a child with a developmental age of at least four years, with insufficient criteria to diagnose irritable bowel syndrome.

- Two or fewer defecations in the toilet per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel motion
- The presence of a large fecal mass in the rectum
- History of large-diameter stools, which may obstruct the toilet
- After appropriate evaluation, the fecal incontinence cannot be explained by another medical condition

**Supplementary Table 2 Reasons for the failure of novel pharmacological agents in clinical trials**

- Including children from tertiary care centers with severe constipation
- Not insisting on toilet training as a part of the standard care package, especially in young children
- Not addressing other behavioral problems of the child/family
- Heterogeneity of pathophysiology, which cannot be addressed by the drug
- High response to placebo
- Stringent outcome assessment (including fecal incontinence)
- Using adult criteria to assess outcome (> 3 spontaneous bowel motions/week)
- Using parent-reported outcome measures
- Short trial duration
- Potential differences in pharmacokinetics between children and adults
- Not addressing the potential influence of the intestinal microbiome