Search strategy and study selection

Eligible studies will be randomized placebo controlled IBD trials of biologics which are approved by the FDA for IBD treatment (anti-TNFs and/or anti-integrins), or RCTs comparing biologic-immunomodulator combination treatment versus immunomodulator alone (with placebo biologic). To be included, trials outcomes should include clinical efficacy measures as one of the end-points assessed and reported (i.e. purely pharmacokinetic or safety trials not assessing clinical efficacy will be excluded). CD trials for indications other than active luminal CD will be excluded. Discontinuation, post-surgical prophylaxis and combination-biologics trials will be excluded. Duration of biologics therapy will have to be at least two doses of induction spanning = 2 weeks. Therefore, trials using a single infusion or injection of a biologic will be ineligible. A trial employing a single infusion/injection for induction, whether randomized or not, followed by randomization for maintenance phase will be eligible for analysis restricted to efficacy outcomes of the maintenance treatment phase. Studies investigating dosing which are not approved for clinical practice or exploring non-approved indications will be also excluded. Studies with high-risk of bias (see below) will also be excluded. As all studies included in the meta-analysis will be randomized clinical trials, inclusion and exclusion of individual patients will be based on the original inclusion/exclusion criteria of the respective trials. In all trials intention-to-treat population outcomes will be analyzed.

Studies will be identified using existing Cochrane systematic reviews [Bickston CJ, Cochrane Database Syst Rev 2014, CD007571, Macdonald JK, Cochrane Database Syst Rev 2007, CD006097, Behm BW, Cochrane Database Syst Rev 2008 CD006893, Lawson MM Cochrane Database Syst Rev 2006 CD005112 ], AGA technical review [Dassopoulos T, Gastroenterology 2013] and ECCO guidelines [Dignass A, JCC 2012, Dignass A, JCC 2010]. These will be supplemented by a search of the medical English literature conducted with MEDLINE (1976 to November 2015) and EMBASE (1991-2015) databases. Eligible studies will be identified using the term string: (Crohn's disease or ulcerative colitis or inflammatory bowel disease or IBD) combined with the set operator AND with studies identified by the term string: (trial or randomized or placebo), and conjointly combined with the set operator AND with the term string: (infliximab or CA2 or adalimumab or D2E7 or certolizumab or CDP870 or golimumab or CNTO148 or natalizumab or vedolizumab or MLN02 or MLN0002 or LDP-02 or anti-TNFa or anti tumor necrosis factor OR TNFa inhibitor or tumor necrosis factor inhibitor or antibody to tumor necrosis factor or tumor necrosis factor

alpha or antibody to alpha4 or anti-alpha4 or antibody to integrin or anti-VLA4 or anti-VLA-4 or anti-integrin). This search will be further supplemented by search of the Cochrane CENTRAL register of controlled trials and the Cochrane IBD Group Specialized Trials Register using the terms 'Crohn's disease' and 'Ulcerative colitis'. In addition, clinical trials registry (Clinicaltrials.gov) will be searched using all developmental and generic drug names, as specified above, for the approved biologics.

Abstracts of the papers identified by the initial search will be evaluated for appropriateness to the study question, and all potentially relevant papers will be obtained and evaluated in detail. Abstract proceedings from Digestive Diseases Week, United European Gastroenterology Week, and the European Crohn's and Colitis Organization between 2007 and November 2015 will be hand-searched to identify potentially eligible studies published only in abstract form. The citation lists of identified relevant studies will be used for performing a further cross-search of the literature. Articles will be assessed independently by two investigators according to the pre-defined eligibility criteria. Any disagreements between investigators will be resolved by discussion.