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Expert recommendation

Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards

In the format provided by the authors and unedited

Supplementary Box 1 | Review and specialist recommendation process

The review and specialist recommendation project were initiated in December 2021. We subsequently collected evidence based on three systematic reviews and complemented those data by additional literature as highlighted in the manuscript. The project draft was discussed among several specialists in the field of monogenic IBD in January 2022 and additional specialists were invited. The selection of the final expert group was based on the following criteria: expertise documented by key contributions to literature on monogenic IBD or primary immunodeficiencies that can present with intestinal inflammation, or IBD genetics or IBD related trial design in paediatrics or adults.
This included contributors in the field of monogenic IBD (AM, SS, CK, FR, DS, DK, YH, HU), paediatric and adult trials specialists (DT, AG, MD, SK, DW, LDR, ST), as well as immunologists/transplantation specialists and gene therapy experts (CK, CB, SH, AO, M, BG). Several members of the group have experience in guideline development in paediatric and adult IBD (DT, AG, MD, SK, DW, LDR, KJ, HU, ST).

To ensure a balanced view of different research fields and health care systems, we had representation of specialists from strong research communities in the UK, Germany, France, Netherlands, US, Canada, Israel, Poland, China, Japan, Qatar, Turkey. This project included specialists from several research consortia (including VEOIBD consortium, COLORS in IBD, Genius group). The group includes physicians as well as non-clinical specialists at different career stages. A patient with experience of mIBD and many experimental therapies before a successful allograft was included in the working group and discussion of recommendations but preferred not to be acknowledged by name.

As a consequence of this selection process this group of investigators involved 26 clinicians and scientists.

After review of the literature and sharing the literature summary, we outlined a draft proposal and invited comments and revisions.
After selection of the specialist group, both the outline of the draft analysis and draft recommendations were extensively discussed via e-mail, teleconference, and in person. A first set of 5 initial recommendations were voted upon in April 2022 via anonymous electronic voting. The analysis of First Voting was completed 23.04.2022 (Supplementary Table 1 1, participation rate at the vote 61%; 2 of the 5 votes received nominal 80% pass rate).
The results and comments were shared with the group and discussed in a set of subsequent phone conferences to discuss the results with the participants from different time zones (25th and 28th May 2022). As a consequence of the votes, the comments and the discussions, we recognised that key therapeutic goals need to be better defined, and recommendations for off-licence applications, retrospective and prospective studies needed to be adjusted.
A set of 6 adjusted recommendations was derived and voted upon via anonymous electronic voting (26 of the participants voted, 100%; all 6 of the votes reached 80% pass rate; Supplemental table 2). Minor adjustments of the wording were suggested by the participants and communicated to all participants without objections and need to repeat the vote. The final recommendations were shared with all participants (Box 2).

We shared the paper and recommendation and invited feedback from patient organisations and charities representing paediatric and adult patients with IBD and monogenic IBD disorders including Crohn's in Childhood Research Association (CICRA), the X-linked Lymphoproliferative Syndrome (XLP) Research Trust and the Chronic Granulomatous Disorder (CGD) Society.
Based on the comments of the editor and the reviewer, we revised the manuscript and shared again with the three patient support organisations.

Supplementary Table 1 | Analysis First Voting completed 23-04-2022

Recommendation and key comments received	Vote (total and 5 Likert scale from strongly agree to strongly disagree)
Therapeutic goals in patients with mIBD should reflect intestinal inflammation and disease-specific extraintestinal manifestations Key comments raised by the participants: Quality of Life (QoL) matters most, although QoL generally tracks intestinal inflammation - and perhaps extraintestinal manifestations. Some extraintestinal manifestations in mIBD (eg lymphoma) will be uncommon, so the power of the statement will be affected by numbers Key is to reduce systemic inflammation and cancer risk. QoL matters, although likely to track improvement in inflammation/EIMs The spectrum is wide and disease maybe quite refractory to the commonly prescribed immunosuppressors, so this will not always be achievable.	16 responses 7-5-1-2-1
Therapeutic goals for inflammatory bowel disease (i.e. to achieve clinical response, enable growth in paediatric patients, achieve endoscopic healing and histologic remission, normalize inflammatory biomarker, and improve quality of life as outlined by STRIDE-II) do apply for patients with monogenic IBD Comments: ➢ Histological healing is not a formal target in STRIDE-II ➢ Suggest deleting "Histological remission" ➢ Probably. The weight of the STRIDE guidelines is light on evidence ➢ Goals used in adult practice are not validated in paediatric patients, especially in very young patients and specifically in patients with monogenic IBD ➢ concern is "endoscopic healing and histologic remission."	16 responses 8-5-2-1-0
Off-license treatment of patients with mIBD in clinical practice is best documented using mIBD REPORT standards, to assess whether universal IBD treating targets are met, to record adverse events, and to compare a patient's response with medications in the patient's history and published interventions Comments: ➢ For being the first to define standards for reporting that can be universally applied and for want of anything better ➢ 'treatment targets' (not treating)	16 responses 8-5-0-0-3
Observational studies, including case reports, on therapies in patients with mIBD should report standardised outcomes; mIBD REPORT standards can complement study-specific outcome measures and may provided as supplemental information Key comments: ➢ need to recognise the innate bias of this informed voting group ➢ 'may be provided' ➢ Ideally yes, but this is a heterogenous group of patients	16 responses 9-4-0-3-0

Prospective clinical trials that focus on mIBD or will as part of the study population likely recruit patients with mIBD are encouraged to implement mIBD REPORT standards either as secondary outcome measures, or to collect and report mIBD REPORT parameters in those patients as supplemental data Key comments: For all the reasons above, but beware that this can be seen as self serving - so people may disagree on principle! Grammar needs amending - 'supplemental information' or supplemental data' two types of studies could be separated. While I strongly agree with the statement Re: "clinical trials that focus on mIBD," the second type of study (will as part of the study population likely recruit patients with mIBD) looks different. For the latter case, it may be difficult for a clinical trial to implement "all" mIBD REPORT criteria in the trial protocol at the outset. Because you will need to determine a set of criteria to assess response for only a subset of patients that may or may not be included in the trial, which will make the trial complicated.	16 responses 8-4-1-3-0

Supplementary Table 2: Second vote analysis 23-5-2022

Recommendation	Vote (total and 5 Likert scale from strongly agree to strongly disagree)
1. Therapeutic goals for treating patients with mIBD should reflect the individual patient's health related quality of life (including emotional and social functioning, intestinal and extra-intestinal inflammatory problems etc.) as well as disorder-specific prognostic considerations (e.g. infection susceptibility, organ damage due to autoimmunity, need for enteral and parenteral nutrition, development and growth, tumour susceptibility, impact of available therapies etc.)	(Agreement 96%) 26 responses 23-2-0-0-1
2. In principle, the therapeutic goals defined for conventional inflammatory bowel disease do apply for patients with monogenic IBD (e.g. to achieve clinical and endoscopic remission, to normalize inflammatory biomarker; to improve quality of life and to enable growth); treatment options need to be considered since these therapeutic goals may be challenging to achieve, some of the tools to assess response to therapy may not be valid in the youngest age group, and treatment of extraintestinal disease needs to be balanced	(Agreement 96%) 26 responses 18-7-1-0-0
3. mIBD REPORT standards are a set of parameters (genetics, phenotype, intestinal inflammation and extraintestinal disease, treatment and adverse events) aiming to characterise the patients disease burden and activity at baseline and describe the intestinal response to therapy over time (there is insufficient evidence for uniform outcome targets based in mIBD that affect disproportionally very young patients; components of the mIBD REPORT parameters will be of differential value for individual disorders; additional parameters might be relevant to characterise disease activity for the individual patient and disorder)	(Agreement 92%) 26 responses 19-5-1-1-0
4. Off-license treatment of patients with mIBD in clinical practice should be documented via mIBD REPORT standards to assess whether universal IBD	(Agreement 92%) 26 responses

treatment goals are achieved; a standardised documentation will allow to compare a patient's response with response to medications in the patient's history as well as with published interventions	20-4-1-0-1
5. Observational studies, including case reports, on therapies in patients with mIBD should report standardised outcomes; mIBD REPORT standards may complement study-specific parameters and those may be provided as supplemental information	(Agreement 96%) 26 responses 16-9-0-0-1
6. Performers of prospective clinical trials that investigate therapies for intestinal inflammation in patients with monogenic disorders are encouraged to implement mIBD REPORT standards either as outcome measures, or to report mIBD REPORT parameters as supplemental information; in prospective trials not focusing on intestinal disease but likely recruiting patients with mIBD it is encouraged to collect mIBD REPORT standards as descriptive supplemental information	(Agreement 96%) 26 responses 20-5-0-0-1