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# Ulcerative Colitis: Developing Drugs for Treatment Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document contact Kelly Richards at 240-402-4276.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**April 2022  
Clinical/Medical**

# Ulcerative Colitis: Developing Drugs for Treatment Guidance for Industry

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10001 New Hampshire Ave., Hillandale Bldg., 4th Floor  
Silver Spring, MD 20993-0002  
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)*

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***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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1 **Ulcerative Colitis: Developing Drugs for Treatment**  
2 **Guidance for Industry<sup>1</sup>**  
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6  
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
11 for this guidance as listed on the title page.  
12

13  
14  
15 **I. INTRODUCTION**  
16

17 The purpose of this guidance is to help sponsors in the clinical development of drugs to treat  
18 adults with ulcerative colitis (UC).<sup>2</sup> This guidance addresses the Food and Drug  
19 Administration's (FDA's) current recommendations on clinical trials for drugs being developed  
20 under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), section 351 of  
21 the Public Health Service Act (42 U.S.C. 262) and 21 CFR parts 312, 314, and 601 for treating  
22 UC. Specifically, this guidance addresses FDA's current thinking about the necessary attributes  
23 of clinical trials for drugs being developed for treating UC, including trial population, trial  
24 design, efficacy considerations, and safety assessments.<sup>3,4</sup>  
25

26 This guidance does not address extraintestinal manifestations of UC, pediatric drug development,  
27 or the treatment or prevention of long-term complications of UC (e.g., this guidance is not  
28 intended to discuss endpoints for prevention or reduction in risk of colorectal cancer).  
29

30 This guidance replaces the withdrawn draft guidance for industry *Ulcerative Colitis: Clinical*  
31 *Trial Endpoints* (August 2016).

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<sup>1</sup> This guidance has been prepared by the Division of Gastroenterology (the Division) in the Center for Drug Evaluation and Research at the Food and Drug Administration and the Center for Biologics Evaluation and Research (CBER).

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

<sup>3</sup> In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of drugs to treat UC.

<sup>4</sup> For cellular and gene therapy products, there may be additional considerations. Sponsors should discuss their development program with the Office of Tissues and Advanced Therapies. For clinical trials involving gene therapy products, sponsors should consult the guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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33 The contents of this document do not have the force and effect of law and are not meant to bind  
34 the public in any way, unless specifically incorporated into a contract. This document is intended  
35 only to provide clarity to the public regarding existing requirements under the law. FDA  
36 guidance documents, including this guidance, should be viewed only as recommendations, unless  
37 specific regulatory or statutory requirements are cited. The use of the word *should* in Agency  
38 guidances means that something is suggested or recommended, but not required.  
39

## 40 41 **II. BACKGROUND**

42  
43 UC is a chronic, relapsing, and remitting inflammatory bowel disease characterized by diffuse  
44 mucosal inflammation of the colon.

45  
46 UC involves the rectum, and it may extend proximally in a contiguous pattern to affect part of  
47 the colon or the entire colon. Clinical manifestations of active UC include bloody diarrhea (with  
48 or without mucus), urgency, tenesmus, abdominal pain, weight loss, fever, and malaise. In  
49 patients with extensive or severe inflammation, acute complications such as severe bleeding and  
50 toxic megacolon, which can lead to perforation, may occur (Danese and Fiocchi 2011).

51  
52 The treatment goals of UC include resolution or reduction of the signs and symptoms of active  
53 disease to provide relief to the patient and healing or control of the underlying mucosal  
54 inflammation and its complications.

## 55 56 57 **III. DEVELOPMENT PROGRAM**

### 58 59 **A. Trial Population**

60  
61 Sponsors developing drugs to treat UC should consider the following:

- 62  
63 • Subjects should have a confirmed diagnosis of UC based on documented findings on  
64 endoscopy and histopathology.
- 65  
66 • For clinical trials for drugs intended to treat moderately to severely active UC:
  - 67  
68 – Subjects should have a score of 5 to 9 on the modified Mayo Score (mMS),<sup>5</sup>  
69 including an endoscopy subscore of at least 2.
  - 70  
71 – Sponsors should enroll subjects across the whole range of both moderately and  
72 severely active disease categories.

73

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<sup>5</sup> The *mMS* is a composite endpoint consisting of rectal bleeding, stool frequency, and endoscopy subscores, adapted from the originally published Mayo Score. The previously used physician global assessment component is excluded to reduce subjectivity and focus the evaluation on the subject's directly reported symptoms and directly observable endoscopic findings. See Table 1 in the Appendix.

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74 — We recommend a balanced representation of subjects who have never received  
75 treatment with a biologic and subjects who have failed prior therapy with one or more  
76 biologics or other advanced therapies.

- 77
- 78 • For drugs intended to support an indication of mildly to moderately active UC, sponsors  
79 should enroll subjects with a score of at least 4 on the mMS, including an endoscopy  
80 subscore of at least 2 and a rectal bleeding subscore of at least 1.
  - 81
  - 82 • Sponsors should enroll subjects who reflect the characteristics of clinically relevant  
83 populations, including with regard to race and ethnicity, and should consider clinical trial  
84 sites that include higher proportions of racial and ethnic minorities to recruit a diverse  
85 study population.<sup>6</sup>

### **B. Trial Design**

86

87

88

89 Sponsors developing drugs to treat UC should consider the following:

- 90
- 91 • We recommend a randomized, double-blind, placebo-controlled trial design that would  
92 be able to demonstrate that beneficial effects observed initially with treatment are  
93 continued long term to support chronic administration. This goal may be achieved  
94 through various study designs, and the overall design of a program should be agreed upon  
95 with the appropriate review division before trial initiation.
  - 96
  - 97 — One approach (*induction followed by randomized withdrawal maintenance*) is to  
98 conduct a randomized, placebo-controlled induction trial to assess clinical benefit in  
99 the short term, followed by a maintenance trial in which all subjects who achieve  
100 initial clinical response<sup>7</sup> to active drug at the end of induction are re-randomized to  
101 receive either active treatment or placebo, and efficacy is evaluated again at the end  
102 of the maintenance phase (e.g., 52 weeks).<sup>8</sup>
  - 103
  - 104 — Another approach (*treat-through design*) is to randomize subjects once at the start of  
105 the trial to one of the treatment arms (i.e., a dosing regimen or placebo), and subjects  
106 are then treated continuously without rerandomization through 52 weeks. Sponsor  
107 should assess the primary endpoint at the end of treatment (e.g., 52 weeks). Earlier  
108 periodic assessments throughout the trial are useful to characterize the time to onset  
109 of initial clinical improvement. Early escape criteria should be incorporated to ensure  
110 that subjects who are worsening or not improving after a reasonable time frame have  
111 the opportunity to receive active treatment.

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<sup>6</sup> For additional recommendations, refer to the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

<sup>7</sup> As defined in section C, Efficacy Considerations.

<sup>8</sup> Placebo responders at the end of induction should continue to receive blinded placebo in maintenance. Early escape criteria should be incorporated to ensure that subjects who are worsening or not improving after a reasonable time frame are discontinued from blinded study treatment and offered either rescue dosing or an alternative active treatment.

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- For drugs intended to be administered chronically, we recommend a total controlled treatment period of at least 1 year in duration to adequately assess both early efficacy and durability of response over time and to adequately characterize the safety profile. Sponsors should discuss with the appropriate review division the number of subjects exposed to the to-be-marketed dosing regimen for a minimum of 1 year that should be available at the time of application submission.
  - We encourage active controlled trials designed to demonstrate superiority to an approved therapy.
  - Sponsors can consider noninferiority studies, but we recommend that sponsors reach agreement on an acceptable noninferiority margin with the appropriate review division before initiating clinical trials.<sup>9</sup>

126

127 **C. Efficacy Considerations**

128

129 *1. Efficacy Assessments*

130

131 Sponsors developing drugs to treat UC should consider the following:

132

- We recommend evaluating the proportion of subjects achieving clinical remission as the primary endpoint.
  - **Clinical remission:** Defined as an mMS score of 0 to 2, including the following three components:<sup>10</sup>
    - 1) Stool frequency subscore = 0 or 1<sup>11</sup>
    - 2) Rectal bleeding subscore = 0
    - 3) Centrally read endoscopy subscore = 0 or 1 (score of 1 modified to exclude friability)
  - Sponsors should explore the proportion of subjects in clinical remission who had a stool frequency subscore of 0 versus 1. Although a stool frequency subscore of 0 or 1 is allowable for individual subjects, a subscore of 1 in a significant number of subjects may not be considered adequate evidence of stool normalization, and this limitation may be noted in the label.

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<sup>9</sup> For additional information, see the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

<sup>10</sup> See Table 2 in the Appendix for sample instructions for patients to accurately capture patient-reported outcome data for stool frequency and rectal bleeding subscores.

<sup>11</sup> For products intended to treat mildly to moderately active UC, the recommended definition of remission should be modified to include a stool frequency subscore of 0 or 1 and no greater than baseline (start of trial).

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- Although historically sponsors have used sigmoidoscopy for the endoscopic assessment, we recommend that colonoscopy be used to document disease activity in all involved segments of the colon.
  - We recommend using centralized reading of endoscopies as the primary approach to scoring the endoscopic component of the primary and secondary endpoint assessments. Both the endoscopist performing the procedure and the central readers reviewing high-definition video recordings of the procedure should be blinded to treatment assignment and should document the endoscopic findings. The protocol should specify clearly how discrepancies between the findings by the endoscopist and the central reader will be handled in the efficacy analyses (e.g., adjudication by a third reader). Efforts should be made to minimize bias and standardize reading of endoscopy across trial sites and among investigators through training and education on the definition of each item described in the scale. Sponsors should draft charters that standardize procedures, video recordings/equipment, and endoscopy assessment early in drug development and share them with FDA for comment.
  - For calculation of the mMS stool frequency and rectal bleeding subscores (at baseline and prespecified timepoints for efficacy assessment), the following considerations apply:
    - To calculate the stool frequency subscore and the rectal bleeding subscore, we recommend defining a 7-day period during which daily subscores are collected before the specified study visit when the mMS (or partial MS) is calculated.
    - The subscores should be calculated by averaging the daily subscores from within this 7-day period, excluding the day of bowel preparation and day of endoscopy (for visits that include an endoscopy).
    - A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary (otherwise the score should be considered *missing* and the subject's result imputed as nonresponder).
  - We recommend the following secondary endpoints:
    - **Clinical response:**<sup>12</sup> Defined as a decrease from baseline in the mMS of greater than or equal to 2 points and at least a 30 percent reduction from baseline, and a decrease in rectal bleeding subscore of greater than or equal to 1 or an absolute rectal bleeding subscore of 0 or 1.

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<sup>12</sup> Although clinical response is not the final treatment goal, this definition may be used as a criterion at the end of induction to rerandomize subjects who are demonstrating improvement to continue into a maintenance phase in the induction/maintenance design.



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- 194 – **Corticosteroid-free remission:** Defined as subjects who are in clinical remission at  
195 the conclusion of the controlled trial (e.g., 52 weeks) and having no corticosteroid  
196 exposure during a prespecified period (e.g., at least 8 to 12 weeks) before that  
197 assessment.  
198
- 199 The proportion of subjects achieving corticosteroid-free remission, of those who were  
200 using corticosteroids at enrollment, is of interest and should be reported.  
201
- 202 – **Endoscopic improvement:** Defined as a centrally read endoscopy subscore of 0 or 1  
203 (score of 1 modified to exclude friability).  
204
- 205 – **Endoscopic remission:** Defined as a centrally read endoscopy subscore of 0.  
206
- 207 We do not recommend the use of the term *mucosal healing* at this time, as there is no  
208 consensus as to how best to define this concept.  
209
- 210 – **Maintenance of remission:** We recommend the following to demonstrate the  
211 durability of benefit:  
212
- 213 ■ For trial designs in which subjects who achieve clinical response at the end of the  
214 induction phase are rerandomized in the maintenance phase, we recommend that  
215 sponsors assess remission within the subset of subjects who enter the maintenance  
216 phase in remission to support the ability of the therapy to maintain a durable state  
217 of remission.  
218
  - 219 ■ For trial designs in which subjects are treated continuously without  
220 rerandomization (treat-through design), sponsors should assess the proportion of  
221 subjects who individually achieve clinical remission at both early (e.g., 8 weeks)  
222 and late (e.g., 52 week) time points to demonstrate that a clinical benefit was  
223 attained and was durable.  
224
- 225 • We recommend the following exploratory endpoints, each of which should be discussed  
226 with FDA before trial initiation:  
227
- 228 – **Histologic response/remission:** At this time, there is no scientific consensus on a  
229 definition of, or scoring system for, histologic resolution of mucosal inflammation in  
230 subjects who achieved endoscopic remission in UC. Sponsors should provide  
231 adequate justification for the proposed endpoint definitions, grading scales, and  
232 scoring techniques.  
233
  - 234 – **Interim clinical assessments based on noninvasive measures:** Sponsors should  
235 incorporate interim clinical assessments based on the noninvasive components of the  
236 mMS (such as stool frequency and rectal bleeding subscores) at prespecified time  
237 points during the trial, up until and including the last visit (e.g., 52 weeks), to support  
238 maintenance of remission.  
239

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240 – **Additional Endpoints:** We encourage sponsors to explore the effect of an  
241 investigational drug on additional symptoms of UC identified by subjects as  
242 important but that are not captured within the mMS (e.g., abdominal pain, urgency)  
243 using fit-for-purpose patient-reported outcome (PRO) instruments (see section III. C.  
244 3., Future Patient-Reported Outcome Instrument Development).  
245

### 246 2. *Statistical Considerations*

247  
248 Sponsors developing drugs to treat UC should consider the following:  
249

- 250 • To gain precision in evaluating overall treatment effects (e.g., the overall difference in  
251 remission rates), we recommend statistical analyses adjust for subject characteristics at  
252 baseline that may affect efficacy outcomes (e.g., duration of disease, disease severity,  
253 concurrent use of corticosteroids, prior biologic use).  
254
- 255 • Sponsors should conduct efficacy analyses in all randomized subjects.  
256
- 257 • Sponsors should prespecify methods to handle intermittent missing data (e.g., lack of at  
258 least 3 consecutive diary days, or 4 nonconsecutive diary days, during the 7 days before a  
259 visit).  
260
- 261 • Subjects who drop out before the end of treatment should be considered treatment  
262 failures.  
263
- 264 • Sponsors should prespecify a primary estimand of interest for each endpoint and justify  
265 that it is meaningful and that it can be estimated with minimal and plausible assumptions  
266 with the proposed analysis. The estimand is a precise description of the treatment effect,  
267 reflecting the clinical question posed by a given clinical trial objective. See the  
268 International Council for Harmonisation harmonized guideline *E9 R1 Addendum on*  
269 *Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical*  
270 *Principles for Clinical Trials*.<sup>13</sup> The following considerations apply:  
271
  - 272 – The important intercurrent events that should be considered when defining the  
273 estimand include treatment discontinuation attributable to lack of efficacy or adverse  
274 events, use of rescue medication, and UC-related surgery.  
275
  - 276 – Potential strategies for defining and handling intercurrent events include the  
277 following:  
278
    - 279 ▪ A treatment policy strategy in which outcomes are collected after the intercurrent  
280 event and used in analyses.
    - 281
    - 282 ▪ A composite strategy in which subjects who experience the intercurrent event are  
283 considered to have an unfavorable outcome (e.g., to have not achieved remission).

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<sup>13</sup> Available at [https://database.ich.org/sites/default/files/E9-R1\\_Step4\\_Guideline\\_2019\\_1203.pdf](https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf).

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284  
285 — Sponsors should continue to follow subjects after the occurrence of all intercurrent  
286 events, regardless of the strategy used in the primary analysis, to facilitate important  
287 analyses using a treatment policy strategy. The protocol should distinguish between  
288 reasons for treatment discontinuation and reasons for study withdrawal and should  
289 include plans to follow subjects for collection of relevant data after treatment  
290 discontinuation and use of rescue therapies.

291  
292 • Sponsors should prespecify sensitivity analyses to evaluate whether the results from the  
293 primary and secondary analyses are robust to the missing data assumptions. These  
294 sensitivity analyses should comprehensively explore the space of plausible assumptions.  
295

### 296 3. *Future Patient-Reported Outcome Instrument Development*<sup>14,15</sup>

297  
298 • Sponsors wishing to develop additional novel PRO instruments (or adapt existing  
299 instruments for use in UC patients) to assess concepts that are relevant to UC patients but  
300 not captured within the mMS can submit a PRO instrument development proposal for  
301 FDA review.

302  
303 — Sponsors pursuing PRO instrument development may need to collect additional  
304 qualitative information from patients to support the relevance of the selected  
305 symptom(s), and document that patients understand and can use the instrument’s  
306 proposed items.  
307  
308 — To support potential labeling claims, an adequate number of patients should  
309 demonstrate the presence of the additional symptom(s) at baseline, with sufficient  
310 degree of severity in order to be able to measure a clinically meaningful improvement  
311 over the course of treatment.

312  
313 — Additionally, sponsors may need to collect evidence that captures clinically important  
314 improvement at the individual patient level to inform the definition of response using  
315 the PRO instrument, preferably by including anchor-based analyses but also by other  
316 methods.

## 317 **D. Safety Considerations**

318  
319 Sponsors developing drugs to treat UC should consider the following:  
320

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<sup>14</sup> For general recommendations regarding PRO assessments (as well as information relevant for other clinical outcome assessments), see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

<sup>15</sup> For general recommendations regarding PRO assessments (as well as information relevant for other clinical outcome assessments), see the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient’s Voice in Medical Product Development and Regulatory Decision Making web page at <https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical>.

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- In general, FDA has recommended a washout period of 5 half-lives for prior therapies or undetectable serum levels (when available) for trial subjects. To promote timely enrollment of subjects with active disease and reduce the potential need for escalation of corticosteroids as *bridging* therapy, sponsors may propose shorter washout periods, with appropriate justification.
    - Sponsors proposing a shorter washout period should acknowledge within the protocol and informed consent the potential increased risk of adverse events (e.g., serious infections) in the early portion of the trial, and sponsors should include appropriate close monitoring and risk mitigation plans.
  - For drugs intended for long-term treatment, such as for UC, a sufficient number of subjects should be exposed to the to-be-marketed dosing regimen (selected induction dose, followed by selected maintenance dose, when applicable) for at least 52 weeks to characterize the safety profile of the drug.<sup>16</sup>
  - Drug-specific considerations may alter the minimum acceptable size of the safety database, including whether the drug in question is a new molecular entity or has relevant supportive safety data from other populations, the known and anticipated adverse events of the drug and drug class, and nonclinical findings.
  - For trials of therapeutic protein products, such as monoclonal antibodies, sponsors should consider recommendations in the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Sponsors should evaluate neutralizing capabilities of antidrug antibodies and their impact on clinical efficacy and safety.
  - Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, or hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Sponsors should stratify by study any analyses of integrated data from multiple studies.
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<sup>16</sup> For recommendations about duration of exposure and number of patients to be included in the safety database, see the guidance for industry *Premarketing Risk Assessment* (March 2005).

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**REFERENCES**

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**Literature**

Danese S and Fiocchi C, 2011, Ulcerative Colitis, *N Engl J Med*, 365(18):1713–1725.

**Guidances<sup>1</sup>**

Guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020)

Guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)

Guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020)

Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

Guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016)

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009)

Guidance for industry *Premarketing Risk Assessment* (March 2005)

International Council for Harmonisation harmonized guideline *E9 R1 Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials* (November 2019)<sup>2</sup>

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<sup>1</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>2</sup> Available at [https://database.ich.org/sites/default/files/E9-R1\\_Step4\\_Guideline\\_2019\\_1203.pdf](https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf).

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**APPENDIX**

385  
386  
387 The modified Mayo Score (mMS) (see Table 1) is a composite endpoint consisting of rectal  
388 bleeding, stool frequency, and endoscopy subscores, adapted from the originally published Mayo  
389 Score. Table 2 provides an example of instructions for subjects to accurately capture patient-  
390 reported outcome data for stool frequency and rectal bleeding subscores.

391  
392 **Table 1. Modified Mayo Score (mMS)**  
393

<b>mMS Subscores by Category</b>	
<b>Stool Frequency*</b>	
0	Normal number of stools for this patient
1	1–2 more stools than normal
2	3–4 more stools than normal
3	5 or more stools more than normal
<b>Rectal Bleeding**</b>	
0	No blood seen
1	Stool with streaks of blood
2	Stool with more than streaks of blood
3	Blood alone passed
<b>Endoscopy</b>	
0	Normal appearance of mucosa
1	Mild disease (erythema, decreased vascular pattern), no friability
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)

394 \* Each patient provides own baseline against which to compare the degree of abnormality in stool frequency.

395 \*\* Represents the worst bleeding score for that day.

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397 **Table 2. Example of Standardized Instructions for Recording Number of Stools and Worst**  
 398 **Rectal Bleeding (Each in a 24-Hour Period)\***  
 399

Category of Instructions	Specific Instructions to Patients
Definition of <i>stool frequency</i>	<ul style="list-style-type: none"> <li>• Patients should be instructed to report the number of trips to the toilet when the patient had a bowel movement (including passing feces, blood alone, blood and mucus, or mucus only).</li> </ul>
Reference remission stool frequency (in a 24-hour period)	<ul style="list-style-type: none"> <li>• The patient should be asked to identify at the screening visit how many stools he or she had in a 24-hour period when in remission from ulcerative colitis (UC).</li> <li>• If the patient does not report achieving remission, then the patient should be asked to identify the number of stools he or she had in a 24-hour period before initial onset of signs and symptoms of UC. If the patient has not experienced remission, this value will be used to calculate the stool frequency endpoint.                             <ul style="list-style-type: none"> <li>– Sponsors should record if the reference remission stool frequency is based on reported stool frequency when the patient was in remission or reported stool frequency before initial onset of signs and symptoms of UC.</li> <li>– Both the remission and the pre-UC stool frequency should be collected at baseline when feasible. This allows exploration of the natural history of prediagnosis stool frequency versus remission stool frequency.</li> </ul> </li> </ul>
Most severe category of rectal bleeding (in a given 24-hour period)	<ul style="list-style-type: none"> <li>• Patients should be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given 24-hour period.</li> <li>• Categories of rectal bleeding should be defined as follows (in order of increasing severity):                             <ul style="list-style-type: none"> <li>– Not applicable; no bowel movement**</li> <li>– No blood seen</li> <li>– Stool has streaks of blood</li> <li>– Stool has more than just streaks of blood</li> <li>– Blood alone passed</li> </ul> </li> </ul>
Completion of event log or diary	<ul style="list-style-type: none"> <li>• Patients should be trained on the completion of the event log or diary.</li> <li>• The instructions for completion of the stool frequency and rectal bleeding assessments should be incorporated into the event log or diary for ready reference by the patient.</li> </ul>
Recording of rectal bleeding and stool frequency assessments	<ul style="list-style-type: none"> <li>• Patients should be directed to capture their rectal bleeding and stool frequency assessments in event logs or daily diaries for a minimum of 7 days before each visit.</li> </ul>

400 \* FDA encourages sponsors to propose an electronic data collection method (e.g., electronic diary, web-based  
 401 system) as an alternative to pen and paper data collection. If an electronic data collection method is proposed,  
 402 sponsors should provide site training and instructions for subjects and investigators. To minimize missing data,  
 403 sponsors should implement a web- or paper-based backup plan and reminder or alarm functions on the electronic  
 404 device. To ensure proper recall period for the assessment, sponsors should consider exploring inclusion of  
 405 reasonable lock-out times before and after which no entries can be made.

406 \*\* If the event log or diary is set up to include the option of “no bowel movement occurred,” then this rectal  
 407 bleeding response is not necessary.