Document History

Date	Who and what
9/18/2023	Drs. Jacquelyn Powers, Yulia Lin, and David Henry proposed this guideline topic to the ASH Committee on Quality (COQ).
12/21/2023 to 1/8/2024	The ASH Committee on Quality agreed to develop a plan for guidelines on this topic. ASH staff confirmed that the British Society of Hematology and the European Society of Hematology do not have current guidelines or revisions in development on the topic.
2/8 to 2/18/2024	ASH staff Rob Kunkle and Meghin Brooks drafted this plan, incorporating information from the proposal by Dr. Powers and colleagues.
2/20/2024	Reviewed by Drs. Adam Cuker and Matt Cheung. Minor edits. RK and MB added questions to committee and expert reviewers.
2/26/2024	Reviewed by the COQ and the ASH Guideline Oversight Subcommittee. Minor edits by RK.

Plan for New ASH Clinical Practice Guidelines on Iron Deficiency Anemia

In 2024, the American Society of Hematology (ASH) will support development of new guidelines on iron deficiency anemia. This plan describes scope, methods, and timeline.

Background

Iron deficiency anemia is the most common hematologic condition worldwide, affecting individuals across the lifespan and in a variety of settings. Iron is a critical micronutrient that serves key functions throughout the body. Iron deficiency affects erythropoiesis, and over time results in iron deficiency anemia. Patients with persistent, refractory, or recurrent iron deficiency anemia are often referred to hematologists for evaluation and management. The most commonly affected populations include young children and adolescent and adult women. Individuals with underlying gastrointestinal disorders, bleeding disorders, heart failure, and other chronic comorbid conditions are also affected by iron deficiency anemia.

There is wide variation in the use of iron testing (e.g., serum ferritin, transferrin saturation, and/or full iron panel) for screening and diagnosis, and there is disagreement about the thresholds used to diagnose iron deficiency. After diagnosis, there is also uncertainty about and variation in treatment approaches for iron deficiency and iron deficiency anemia, including use of oral and intravenous iron replacement therapies. Over the past 10 years there has been a significant increase in literature on oral iron absorption to inform dosing and frequency of oral iron therapy, availability of new intravenous iron formulations, as well as data on iron parameters to define iron deficiency in different populations. This evidence needs synthesis and evaluation.

Socioeconomic factors and systemic inequities may drive important variation in clinical practice. This evidence needs review and synthesis. There are many existing guidelines and review articles about iron deficiency anemia. Mainly, these resources offer informal recommendations that are not based on systematic reviews of evidence. Some of the most well-known and best developed resources for general populations with iron deficiency anemia include guidelines from the World Health Organization (WHO 2020) and from the British Society of Gastroenterology (Snook et al. 2021). Recommendations about iron deficiency are also offered in guidelines on other diseases or conditions, such as heart disease

(Qaseem et al. 2013), cancer (Aapro et al. 2018), inflammatory bowel disease (Goddard et al. 2011; Ko et al. 2020), or pregnancy (Guidelines & Protocols Advisory Committee, 2019). Resources in development at of the time of this writing include a joint clinical report by Powers and colleagues sponsored by the American Academy of Pediatrics (AAP) and the American Society of Pediatric Hematology/Oncology (ASPHO) on the prevention, diagnosis, and treatment of iron deficiency and iron deficiency anemia in pediatric populations. This report was submitted to ASH for review and feedback, which was incorporated into the final version, awaiting approval by the AAP Board.

ASH guidelines on this topic would address a need for authoritative guidelines for hematologists based on systematic reviews of available evidence.

Scope and Aims

These guidelines will address 10 clinical questions. Each question will be answered by one or more graded recommendations.

Each question will be formulated in a way that it can be answered by a single systematic review of evidence. A standard question will specify a population, a single intervention, and a single comparison. Questions may have multiple comparisons; in this case, each comparison will count as a separate question. For each question, up to 7 outcomes will be analyzed.

The specific questions will be determined by a guideline panel. Potential questions may address the following topics:

- Diagnostic testing, including thresholds for defining iron deficiency in various populations (children, pregnant women, individuals with concomitant inflammation)
- Optimal forms and dosing of oral iron therapy for individuals with iron deficiency and iron deficiency anemia
- Iron therapy for pre-operative anemia related to patient blood management
- Intravenous iron therapy for specific populations

These initial guidelines are not expected to be comprehensive, i.e., not all of the above topics are expected to be addressed by questions and recommendations in these initial guidelines. The guideline panel will prioritize questions with greatest potential impact on quality now. After the questions are formulated, ASH will evaluate if an expanded scope is needed. If so, follow-up guideline efforts may be planned, i.e., additional guidelines on additional aspects of iron deficiency not addressed by the initial guidelines.

Available Evidence

Recent studies have addressed diagnostic thresholds and testing and treatment options including dosing. These studies include cross-sectional studies assessing ferritin thresholds / iron parameters to define iron deficiency/iron deficiency anemia (Mei et al. 2021; Abdullah et al. 2017); prospective studies evaluating iron absorption utilizing iron isotopes in iron deficient women (Moretti et al. 2015; Stoffel et al. 2017); and randomized clinical trials of oral and/or IV iron therapies (Powers et al. 2017; Kiss et al. 2015; Pasricha et al. 2023).

Perspective

These new guidelines will provide recommendations mainly for clinicians in high-resource settings internationally, taking an individual patient perspective (i.e., rather than the perspective of a health system or of policymakers). For each recommendation, remarks or discussion will describe implementation considerations in low-resource settings, facilitating adaptation of the recommendations for low-resource settings and for different perspectives such as by health systems in different countries or regions.

Guideline Panel

ASH will form a single guideline panel of 23 individuals, including a clinical co-chair and a methodology co-chair. The panel will mainly include hematologists who are experts in iron deficiency anemia. The panel may also include experts in clinical biochemistry, obstetrics/gynecology, and other relevant medical specialties. The panel will include 1-2 patient representatives, i.e., individuals with lived experience of the disease, such as a past patient or a caregiver. Ideally, patient representatives will not *also* be physicians. One panelist will be an early career hematologist. At least 1 panelist will represent the perspective of a hematologist who practices in a typical community setting (i.e., not a major research academic setting). At least 1 panelist will have expertise in pediatric hematology. One panelist will have expertise in implementation science.

The panel will be diverse with respect to intellectual point of view on the guideline questions, geography and institution, and demographics. Consistent with the goal of developing recommendations for international audiences, panelists will be considered from North and South America, Europe, Africa, and Asia pacific regions. For practical reasons, and because the guidelines will mainly address high-resource settings, most panelists will be from countries with advanced economies.

Methodology expertise will be provided by the methodology team that supports the panel under a paid agreement with ASH. The principal lead from the methodology team will be invited to serve as the methodology co-chair of the guideline panel.

A member of the ASH Guideline Oversight Subcommittee will serve on the guideline panel as an ex officio member. This individual's role will be to ensure that the guideline development process is conducted in accordance with this project plan and ASH policies and procedures, including ensuring that questions are within scope, reviewing participant disclosures and ensuring adherence to ASH COI policies, and critically reviewing the guideline report for publication.

An early career member of the guideline panel may be asked to serve in a "writer" role. Responsibilities of this role will include drafting background clinical content, recording panel decisions and discussion points, drafting the guideline report, integrating edits by authors into the guideline report, and addressing comments received during public review. At the beginning of the project, panel leadership will discuss and agree with the writer how to appropriately recognize his or her contributions on publication.

At the beginning of the project, panelists with clinical expertise will be designated as primary liaisons and have main responsibility for writing, editing, or reviewing the dissemination and implementation tools described below, e.g., guideline snapshot, teaching slide set, pocket guide, and digital mobile version. At least one panelist will be designated for each tool.

Organizational Collaborators

ASH will not invite other organizations to collaborate in the funding, development, or approval of these guidelines. However, ASH may invite other organizations to recommend experts for the guideline panel, if experts are needed from outside the ASH membership, and to review the guidelines. Example organizations include the American Gynecological & Obstetrical Society and the American Society for Clinical Laboratory Science. ASH will also explore with other relevant organizations opportunities to promote and disseminate the guidelines. In addition to endorsement, this could include announcements, summaries, commentaries, or educational programs about the guidelines.

Methods

ASH will contract with a methodology team to support the guideline development process, including to conduct systematic reviews of available evidence, help the guideline panel interpret evidence and form recommendations, and develop a guideline report for publication. The project will require substantial collaboration between the team, the guideline panel, and ASH staff. The specific roles and responsibilities of all participants in the process are described in Appendix A, Roles and Responsibilities.

Expected methodological challenges include a large number of important clinical questions that will require prioritization; controversy about many aspects of iron deficiency, including thresholds for diagnosis and treatment; and questions for which available evidence may be low certainty.

Through a request for proposal process, ASH will invite methodology teams to propose specific approaches to the above challenges. These specific approaches will be integrated within the following general steps of the ASH guideline development process:

1. ASH forms a guideline panel.
2. The panel prioritizes guideline questions.
3. A methodology team in collaboration with experts on the guideline panel systematically reviews available evidence.
4. The guideline panel reviews and finalizes evidence summaries and forms recommendations.
5. ASH makes the recommendations available for public comment.
6. The guideline panel and the methodology team write a report of the guidelines for publication and dissemination.
7. ASH committees and officers review and approve publication of the guidelines under the imprimatur of ASH.
8. Authors submit the guidelines report to *Blood Advances* for review and publication.

Other general expectations include the following:

The GRADE approach will be used to assess certainty of evidence (Guyatt et al. 2008). The GRADE Evidence-to-Decision framework (Alonso-Coello et al. 2016) will be used to make judgments about the available evidence and form guideline recommendations using standardized language that has well-defined interpretations for clinicians, patients, and policymakers (Izcovich et al. 2020).

Systematic reviews will be conducted according to standards defined by the Cochrane Collaboration or equivalent.

For each guideline question, the best available evidence will be used to make estimates about the health effects of alternative interventions. These estimates, in combination with other judgments, will support recommendations by the guideline panels.

If published direct evidence is not available for a guideline question, the guideline panel may use indirect evidence. For example, if studies are not available showing the effects of an intervention within a prioritized patient population, studies might be found and used that show the effects of the intervention in other, related populations. In this case, the methods team will support the guideline panel to define pragmatic inclusion criteria and methods to identify and use indirect evidence.

If there are no published studies (direct or indirect) to inform a prioritized guideline question, the panel may choose not to answer the question with a recommendation. Alternatively, the panel may base recommendations on unpublished evidence, if the evidence can be systematically collected. For example, unpublished evidence may be collected and synthesized from available registries (Kanter et al. 2021) or from surveys of clinical experts serving on the guideline panel (Mustafa et al. 2021).

In addition to graded recommendations, the guideline panel may offer good practice statements, provided they meet criteria defined by GRADE (Izcovich et al. 2020, Guyatt et al. 2016).

The GRADEPro Guideline Development Tool will be used to summarize evidence, obtain panel voting, and document panel judgments and decisions.

Meetings and Timeline

There will be two in-person meetings of the guideline panel: the first in Q3 2024 to receive orientation and formulate questions, and a second in Q2 2025 to agree on recommendations. Panel meetings will also be held virtually via Zoom. The frequency of virtual meetings will depend on project needs. For some project phases, meetings may occur every other week; for other phases, monthly.

The planned project timeline (approximately 2 years) is as follows:

Step	Total Expected Time (Months)	2024				2025			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Appoint guideline panel	5	■	■	■					
Prioritize guideline questions	1			■					
Finalize scope for systematic reviews	1				■				
Conduct systematic reviews	6					■	■		
Develop recommendations	3						■	■	
Public comment	1							■	
Draft guideline report	3-6							■	■
Organizational review and approval	1								■
Journal review and publication	TBD								–>

Management of Conflicts of Interest

Conflicts of interest of all participants will be managed in accordance with general ASH policies, as described on the ASH website (https://www.hematology.org/about/governance/conflict-of-interest), and with specific ASH policies and procedures determined by the ASH Guideline Oversight Subcommittee. The most recent version of these policies is attached as Appendix B.

Publication Strategy

Publication strategy for the guidelines and any other intellectual property will be determined by ASH, including the ASH Guideline Oversight Subcommittee. As described in Appendix C, the current strategy is to submit and publish all work relating to this project including the guideline reports and systematic reviews within ASH's online-only open access scientific journal, *Blood Advances*. At the beginning of the project, a presubmission inquiry to the editors of *Blood Advances* will describe all planned work. The inquiry and discussions with the editors will be led by the lead authors and by the GOS ex officio member(s) of the panels.

One guideline report is expected.

Systematic reviews may be developed for submission to *Blood Advances* as separate, simultaneous publications. If the reviews are not prepared as separate publications, details about the reviews will be included with the guideline reports as supplements.

Authorship, sponsorship, and acknowledgements of such publications will be in accordance with academic standards and customs and requirements of the journal of publication. ASH authorship criteria for the guidelines are presented as Appendix D.

Dissemination and Implementation

To support understanding and implementation of the guidelines, the panel will be asked to write recommendations and remarks that are clear and actionable.

As recommendations are drafted, ASH staff will work with the chair and panelists to develop a dissemination and implementation plan that will enhance access, for clinician and patients, to the guideline and support understanding and implementation of the guideline's recommendations. The plan will identify expected implementation barriers for specific recommendations, e.g., insufficient clinician awareness or insufficient information systems support. Example products that may be developed to address barriers include an informational handout with messaging tailored for clinician, patient, policymaker, and other stakeholders ("snapshot"); a video interview with the chair highlighting key aspects of the guideline; educational teaching slides; a recorded educational webinar; and a digital summary version of the guidelines for the ASH guidelines app. New activities to support the implementation of the guidelines will also be considered, including the development of both clinician- and patient-facing decision-making materials.

References

Abdullah, et al. Re-evaluation of serum ferritin cut-off values for the diagnosis of iron deficiency in children aged 12-36 months. J Pediatr. 2017;188:287-290.

Alonso-Coello P, Schünemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.

Aapro, M., Beguin, Y., Bokemeyer, C., Dicato, M., Gascón, P., Glaspy, J., Hofmann, A., Link, H., Littlewood, T., Ludwig, H., Österborg, A., Pronzato, P., Santini, V., Schrijvers, D., Stauder, R., Jordan, K., & Herrstedt, J. (2018). Management of anaemia and iron deficiency in patients with cancer: ESMO clinical practice guidelines. *Annals of Oncology*, *29*, iv96–iv110. https://doi.org/10.1093/annonc/mdx758

Djulbegovic B, Hozo I. Formulating management strategies using fast-and-frugal trees (a decision tool to transform clinical practice guidelines and clinical pathways into decision support at the point of care). In Djulbegovic and Hozo's *Threshold Decision-making in Clinical Medicine.* Cancer Treatment and Research 189; 2023. https://doi.org/10.1007/978-3-031-37993-2_5.

Guidelines & Protocols Advisory Committee. (2019, April). *Iron deficiency – diagnosis and management*. BC Guidelines.ca. https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-deficiency#ida-pregnant-women

Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.

Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol. 2016; 80:3-7. doi: 10.1016/j.jclinepi.2016.07.006

Izcovich A, Cuker A, Kunkle R, Neumann I, Panepinto J, Pai M, Seftel M, Cheung MC, Lottenberg R, Byrne M, Plovnick R, Terrell D, Holter-Chakrabarty JL, Djulbegovic B, Hicks LK, Wiercioch W, Nieuwlaat R, Schünemann HJ; A user guide to the American Society of Hematology clinical practice guidelines. Blood Adv 2020; 4 (9): 2095–2110.

Kanter J, Liem RI, Bernaudin F, Bolaños-Meade J, Fitzhugh CD, Hankins JS, Murad MH, Panepinto JA, Rondelli D, Shenoy S, Wagner J, Walters MC, Woolford T, Meerpohl JJ, Tisdale J; American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv* 2021; 5 (18): 3668–3689.

Kiss, et al. Oral iron supplementation after blood donation: a randomized clinical trial. JAMA. 2015;313(6):575-83.

Ko, C. W., Siddique, S. M., Patel, A., Harris, A., Sultan, S., Altayar, O., & Falck-Ytter, Y. (2020). AGA clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia. *Gastroenterology*, *159*(3), 1085–1094. https://doi.org/10.1053/j.gastro.2020.06.046

Mei, et al. Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional survey. Lancet Haematol. 2021;e572-e582.

Moretti, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015;126(17):1981-9.

Mustafa RA, Garcia CAC, Bhatt M, Riva JJ, Vesely S, Wiercioch W, Nieuwlaat R, Patel P, Hanson S, Newall F, Wiernikowski J, Monagle P, Schünemann HJ. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol. 2021 Sep;137:231-235. doi: 10.1016/j.jclinepi.2021.02.026. Epub 2021 Mar 3. PMID: 33675954.

Pasricha SR, Mwangi MN, Moya E, Ataide R, Mzembe G, Harding R, Zinenani T, Larson LM, Demir AY, Nkhono W, Chinkhumba J, Simpson JA, Clucas D, Stones W, Braat S, Phiri KS. Ferric carboxymaltose versus standard-of-care oral iron to treat second-trimester anaemia in Malawian pregnant women: a randomised controlled trial. Lancet. 2023 May 13;401(10388):1595-1609. doi: 10.1016/S0140-6736(23)00278-7. Epub 2023 Apr 21. PMID: 37088092; PMCID: PMC10193370.

Powers, et al. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: A randomized clinical trial. JAMA. 2017;317(22):2297-2304.

Qaseem, A., Humphrey, L. L., Fitterman, N., Starkey, M., & Shekelle, P. (2013). Treatment of anemia in patients with heart disease: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *159*(11), 770. https://doi.org/10.7326/0003-4819-159-11-201312030-00009

Snook J, Bhala N, Beales ILP, et al. Gut 2021;0:1–22. doi:10.1136/gutjnl-2021-325210.

Stoffel, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomized controlled trials. Lancet Haematol. 2017;4(11):e524-533.

World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: WHO; 2020. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240000124