An Roinn Sláinte
Department of Health

Unexpected Intraoperative Life Threatening Haemorrhage

National Clinical Guideline No. 29

Annex A: Clinical Guidelines for the Management of Massive Haemorrhage – A systematic review.

National Patient Safety Office
Oifig Náisiúnta um Shábháilteacht Othar

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

CICER
Collaboration in Ireland for Clinical Effectiveness Reviews

Clinical Guidelines for the Management of Massive Haemorrhage–

A systematic review

June 2020

Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

HRB Health Research Board

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

RCSI

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About HRB-CICER

In 2016, the Department of Health requested that the Health Research Board (HRB) fund an evidence synthesis service called HRB-CICER (Collaboration in Ireland for Clinical Effectiveness Reviews) to support the activities of the Ministerial appointed National Clinical Effectiveness Committee (NCEC). Following a competitive process, the Health Information and Quality Authority (HIQA) was awarded the contract for the five-year period from 2017 to 2022. The HRB-CICER team comprises a dedicated multidisciplinary research team supported by staff from the Health Technology Assessment (HTA) team in HIQA and the HRB Centre for Primary Care Research at the Royal College of Surgeons in Ireland (RCSI), as well as national and international clinical and methodological experts.

With regard to clinical guidelines, the role of the HRB-CICER team is to independently review evidence and provide scientific support for the development, by guideline development groups, of National Clinical Guidelines for the NCEC. The HRB-CICER team undertakes systematic reviews of the clinical effectiveness and cost-effectiveness of interventions included in the guidelines as well as estimating the budget impact of implementing the guidelines. The HRB-CICER team also works closely with the guideline development groups; provides tailored training sessions; assists in the development of clinical questions and search strategies; performs systematic reviews of international clinical guidelines and supports the assessment of their suitability for adaption to Ireland; and supports the development of evidence-based recommendations informed by the evidence produced by HRB-CICER within the National Clinical Guidelines.

Membership of the evaluation team

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List of abbreviations that appear in this report

AGREE-II	Appraisal of Guidelines for Research and Evaluation Two Tool
AAGBI	Association of Anaesthetists of Great Britain and Ireland
ANBA	Australian National Blood Authority
ASA	American Society of Anesthesiologists
BCSH	British Committee for Standards in Haematology
GDG	Guideline development group
GRADE	Grades of Recommendations, Assessment, Development and Evaluation
HEMOMAS	Amalgamation of the Spanish Societies of Anesthesia and Resuscitation, Intensive and Critical Care Medicine and Coronary Units, and Thrombosis and Hemostasia
HRB-CICER	Health Research Board – Collaboration in Ireland for Clinical Effectiveness Reviews
ISTMI	Italian Society of Transfusion Medicine and Immunohematology
NBUG	National Blood Users Group (Ireland)
NCEC	National Clinical Effectiveness Committee
NCG	National Clinical Guideline
PICO	Population, interest, context, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organisation

1 Background

1.1 Description of the condition

Intraoperative massive haemorrhages can arise from a number of influences such as index admission bleeding, insufficient surgical control, pathological origins or treatment complications,[1] and have the potential for significant morbidity and mortality.[2] There is no universally accepted definition of a massive haemorrhage, however broad descriptions have been suggested including;[3]

1. Loss equivalent to a person's total blood volume in a 24-hour period.
2. Loss equivalent to 50% of a person's total blood volume over a three-hour period.
3. Loss of blood volume at a rate of 150ml/minute.

The Unexpected Intraoperative Life Threatening Haemorrhage guideline development group (GDG) has provisionally adopted the following description of intraoperative massive haemorrhage: intraoperative bleeding that is catastrophic in nature and difficult to control even for an experienced practitioner. In broad terms, it is associated with clinical features including tachycardia (greater than 110 beats per minute),[3] hypotension (less than 90mmHg systolic blood pressure)[3] and suggests a sudden loss of at least 50% of a person's blood volume. Intraoperative massive haemorrhage does not encompass slow haemorrhage which presents without sudden or acute onset of these clinical signs.

All surgical procedures carry a risk of haemorrhage which can range from anticipated, such as in major cardiac or hepatic procedures, to unexpected in more routine surgeries where large quantities of blood loss are not typically predicted.[4] An intraoperative massive haemorrhage that occurs during surgery and is unanticipated may fall within the definition of an adverse event in the hospital setting.[5] Adverse events present a significant threat to patient safety,[6, 7] with surgical care, and specifically care provided in operating theatres, associated with a notably high incidence of adverse events,[6] and haemorrhage being a frequently encountered complication.[7] Intraoperative massive haemorrhage is an adverse event of key concern in healthcare delivery due to its potential for patient morbidity and mortality.

1.2 Description of the intervention

Patient safety is a fundamental consideration in healthcare policy and delivery, with a growing emphasis on strategies to promote safety and reduce adverse events across the continuum of care, for example the World Health Organisation Patient Safety initiative.[8] Such strategies encompass a proactive move from personnel-centred to system-centred approaches, where

complications or errors are mitigated by well-organised procedures and strategies.[6, 9]

The management of massive haemorrhage requires highly coordinated care provided by a multidisciplinary team including, but not limited to; nurses, surgeons, anaesthetists, radiologists, haematologists and laboratory technicians.[3] In Ireland, guidance exists with regards to management of massive haemorrhage from the National Blood Users group produced in 2002 however, it is of limited relavence to intraoperative massive haemorrhages.[10] Specifically for massive haemorrhages which occur intraoperatively, no national guidance exists regarding strategies and pathways for prevention, recognition or management upon occurrence. Of key concern is the lack of guidance on strategies regarding the timely recognition of an intraoperative massive haemorrhage, the organisational aspects of management, the surgical intervention required and the audit of management as a whole.

1.3 Purpose of this systematic review

The Minister for Health mandated, as a matter of priority, the commissioning and quality assurance of a National Clinical Guideline (NCG) for Unexpected Intraoperative Life Threatening Haemorrhage through the National Clinical Effectiveness Committee (NCEC). A GDG has been established to develop this NCG for the Irish healthcare system. This NCG will focus on the prevention, recognition and management of intraoperative massive haemorrhage in adults. The NCG will not apply to intraoperative massive haemorrhage that is the result of obstetric- or acute trauma-related causes.

The purpose of this systematic review is to identify and appraise clinical guidelines, which make reference to the management of massive haemorrhage, to support the work of the Unexpected Intraoperative Life Threatening Haemorrhage GDG. This review is being conducted to ascertain if there are existing high-quality guidelines with recommendations that could be potentially adopted or adapted for the Irish setting, or if *de novo* development is required.[11]

2 Methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[12]

2.1 Review Question

This systematic review aims to answer the following question:

- What recommendations do clinical guidelines, which make reference to the management of massive haemorrhage, make relating to one or more of the following topics?

- Recognition of massive haemorrhage
- Organisational aspects of massive haemorrhage management (use of protocols, communication, training of personnel)
- Surgical management of massive haemorrhage
- Audit of management

In addition, the definition or description of massive haemorrhage used by each included guideline was extracted.

From preliminary scoping work conducted, it was anticipated that few guidelines specific to massive haemorrhages which occur during the intraoperative period would be identified. Therefore this review question relates to clinical guidelines which make reference to the management of massive haemorrhage broadly and are not specific to any procedure, technique or clinical population (inclusive of trauma, obstetrics and gastrointestinal bleeding). The topics of interest were highlighted by the GDG as potentially valuable to inform recommendations in the NCG. Clinical guidelines were defined as 'Systematically developed statements about specific health problems, intended to assist partictioners and patients in making decisions about appropriate health care', as per the ADAPTE collaboration definition.[11] The modified PICO for the research question is provided in Table 2.1.

Table 2.1 Modified PICO

Population	Adults (aged ≥ 18 years) experiencing massive* haemorrhage
Interest	Recommendations on massive* haemorrhage (which is not specific to any procedure, technique or clinical population) relating to one or more of the following topics: ▪ Recognition of massive haemorrhage ▪ Organisational aspects of massive haemorrhage management (use of protocols, communication, training of personnel) ▪ Surgical management of massive haemorrhage ▪ Audit of management
Context	Clinical guidelines (international or national)
Search period	2000 to September 2019

*Note: Or a related synonym such as major, critical, excessive, severe, profound or catastrophic.

2.2 Search strategy

Electronic searches were conducted in PubMed, Embase, CINAHL (via Ebsco), and The Cochrane Library. The search terms are provided in Appendix 1 and included database specific thesauri and free-text terms. This search strategy was created *de novo* by the research team and used an expansive approach to identify as many potentially relevant guidelines as possible. Grey literature sources were also searched including guideline repositories, guideline developer websites and specific clinical specialty websites. The full list of grey literature sources is provided in Appendix 2. Members of the GDG were also consulted to identify relevant national and international clinical guidelines based on their expert knowledge.

2.3 Eligibility criteria

The specific inclusion and exclusion criteria for this systematic review are provided in Table 2.2. Clinical guidelines were only included if they referred to the management of massive haemorrhage in the broad context and were not specific to a procedure, technique or clinical population (inclusive of trauma, obstetrics and gastrointestinal bleeding).

Table 2.2 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Guidelines of massive* haemorrhage that: ▪ Provide recommendations relating to one or more of the following: Recognition, Organisational aspects, Surgical management, Audit of management ▪ Are novel or adapted from another guideline	Guidelines of massive* haemorrhage that: ▪ Refer to a specific procedure, technique or clinical population (inclusive of trauma, obstetrics and gastrointestinal bleeding) ▪ Are adopted directly from another guideline ▪ Have been archived or are superseded by a more recent version ▪ Were produced before 2000 to ensure identified guidelines are applicable to current practice.

*Note: Or a related synonym such as major, critical, excessive, severe, profound or catastrophic.

2.4 Selection of eligible guidelines

All citations identified from the collective search of electronic databases, grey literature sources and GDG consultation were exported to EndNote® (Version X8) for reference management, where duplicates were identified and removed. Using Covidence®, two reviewers independently reviewed the titles and available summaries of the remaining citations to identify those which warranted full-text review. The full texts were obtained and independently evaluated by two reviewers applying the defined inclusion and exclusion criteria. Where disagreements occurred, discussions were held to reach consensus and where necessary, a third reviewer was involved. Citations excluded during the full-text review stage were documented alongside the reasoning for their exclusion and included in a study flow diagram. Where non-English guidelines were returned, authors were contacted to identify whether an English version was available. If an English translation was not available or the author did not reply the guideline was excluded.

2.5 Data extraction and management

Data extraction was performed independently by two members of the research team. Where disagreements occurred, discussions were held to reach consensus. Relevant information from each clinical guideline was extracted including the definition or description of massive haemorrhage, details of the evidence-base, methods used to formulate recommendations and the specific recommendations of interest to the Intraoperative Massive Haemorrhage GDG. Where a structured process of development was not described in detail within the guideline document, authors were contacted to request this information. Data extraction was conducted in Microsoft Excel, using a data extraction table.

2.6 Quality appraisal

Two reviewers independently assessed the quality of the included guidelines using the Appraisal of Guidelines for Research and Evaluation Two (AGREE-II) tool.[13] AGREE-II scores were calculated and reported as scaled domain scores in accordance with the AGREE-II manual.[13] Inter-rater agreements were assessed by subtracting the scores of the two reviewers; differences of more than two for any item were discussed to reach consensus.

2.7 Currency of guidelines

As recommended by the ADPATE methodology,[11] currency of the included guidelines was assessed by reviewing the guideline publication date and the dates covered by the most

recent evidence search, to ascertain whether the most current evidence had been included.

2.8 Data synthesis

A narrative synthesis of the included clinical guidelines was performed including the definition or description of massive haemorrhage, the recommendations of interest to the GDG, the appraisal of quality and the assessment of currency.

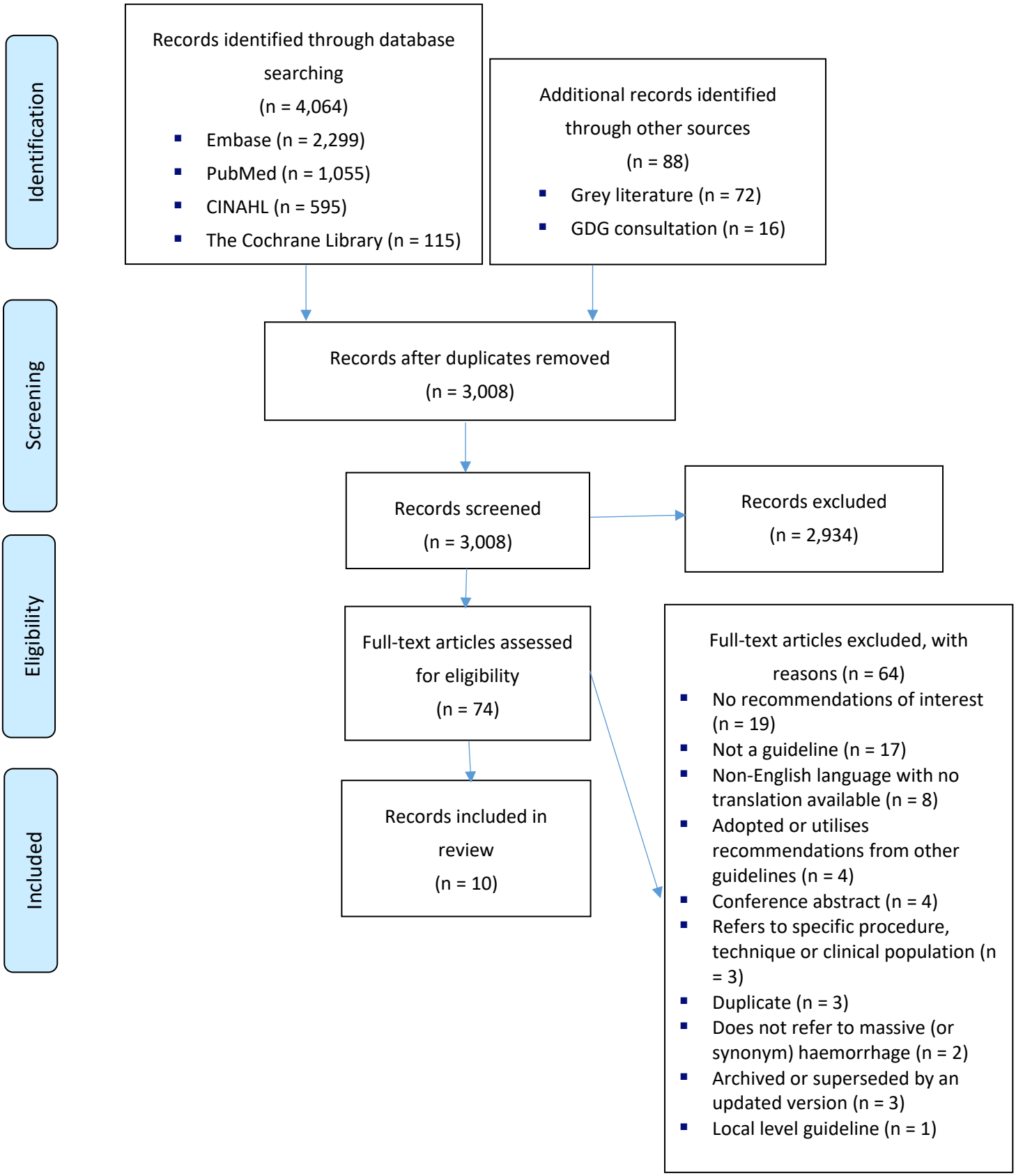
3 Results

3.1 Search Results

The search of electronic databases was conducted on the 26 and 27 September 2019 (Appendix 1). Grey literature sources were searched from the 27 September 2019 to the 2 October 2019 (Appendix 2). Following email consultation, members of the GDG identified a number of potentially relevant guidelines which were added to the screening process (Appendix 2), all of these were simultaneously captured within the searches of electronic databases and grey literature.

Collectively, the searches identified 4,152 citations. After removal of duplicates, the titles and available summaries of 3,008 citations were independently screened by two reviewers and 2,934 records excluded. A total of 74 full-texts were independently assessed by the two reviewers applying the predefined inclusion and exclusion criteria (Table 2.2). Sixty-four records were subsequently excluded at this stage, a detailed overview of the reasons for exclusion is provided in Appendix 3. This resulted in nine clinical guidelines and one associated systematic review being included in this review. A PRISMA flow-chart summarising the search process and subsequent results is provided in Figure 3.1.

Figure 3.1 PRISMA flow diagram



3.2 Guideline characteristics

Nine guidelines[10, 14-21] and one systematic review[22] associated with a guideline were included in this review. An overview of the characteristics of the nine guidelines is provided in Table 3.1. The management of massive haemorrhage was the primary topic for five of the included guidelines,[10, 15, 16, 18, 20] with three being blood transfusion guidelines that referenced massive haemorrhage,[14, 17, 19] and the final guideline concerning safe surgical care.[21]

3.2.1 Origin and developers

Three guidelines were produced in the UK with two from the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[14, 20] and one from the British Committee for Standards in Haematology (BCSH)[15] within the British Society of Haematology. One Irish guideline was produced by the National Blood Users Group (NBUG).[10] The remaining guidelines were from the US by the American Association of Anesthesiologists (ASA),[17] Italy from the Italian Society of Transfusion Medicine and Immunohaematology (ISTMI),[19] Spain by an amalgamation of three societies to form the HEMOMAS group[16] and an international guideline produced the World Health Organisation (WHO).[21] The final guideline originated in Australia from the Australian National Blood Authority (ANBA)[18] and had an associated systematic review published by McQuilten et al.[22] in 2015 with the aim of updating a selected portion of the original evidence base.

3.2.2 Methods to obtain evidence and formulate recommendations

The evidence base used to formulate the recommendations varied across guidelines with five guidelines acknowledging the use of a systematic search for relevant literature in combination with consensus agreement,[15-18, 21] one guideline describing a systematic review alone,[19] one utilising consensus only[20] and two guidelines not providing any information regarding the evidence base.[10, 14] Varying descriptions of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were utilised by three of the guidelines[15, 16, 19] to guide the certainty of the evidence and the strength of recommendations. Four guidelines classified the certainty of the evidence or the strength of recommendations based on other predefined scales,[10, 17, 18, 21] with two guidelines not reporting any methodology.[14, 20]

Table 3.1 Characteristics of included guidelines

Country Year	Associated society or body Primary author	Primary topic of guideline	Development Process	Details of evidence base Search dates	Certainty of evidence and strength of recommendations
United Kingdom 2016	The Association of Anaesthetists of Great Britain and Ireland (AAGBI) **Author:** Klein et al.[14]	Blood transfusion across the hospital system	Updated guideline bringing together 3 previous AAGBI guidelines from 2005, 2008 and 2010. No direct reference made to mentioned guidelines or information provided on methods utilised to formulate recommendations from the existing guidelines.	No information provided	No information provided
United Kingdom 2015 Reviewed 2017 (Addendum added) Planned update-expected completion 2021	British Committee for Standards in Haematology (BSCH) British Society of Haematology **Author:** Hunt et al.[15]	Haematological management of major haemorrhage in any clinical situation	Review of relevant literature with quality of evidence and expert consensus used to generate strength of recommendations. Draft of guidelines reviewed by British Committee for Standards in Haematology Transfusion and Thrombosis and Haemostasis Task forces, The Royal College of Anaesthetists and the Association of Anaesthetists. Circulated to 50 UK Haematologists.	Search of National Health Service Blood and Transplant Systematic Review Initiative Transfusion Evidence Library, PubMed and Embase **Search dates:** Articles published up until April 2015	GRADE criteria as described by Guyatt et al.[23] (2006): **Strength of recommendation:** Grade 1: Strong recommendation made with confidence that the benefits do or do not outweigh the harm and burden of cost of a treatment Grade 2: Suggested recommendation where the magnitude of benefit is less certain **Quality of evidence**: A: High quality randomized control trial B: Moderate quality C: Low quality

Country **Year**	**Associated society or body** **Primary author**	**Primary topic of guideline**	**Development Process**	**Details of evidence base** **Search dates**	**Certainty of evidence and strength of recommendations**
					D: Very low, expert opinion however no information provided regarding method to generate expert opinion
Spain 2015	The Spanish Society of Anesthesia and Resuscitation The Spanish Society of Intensive and Critical Care Medicine and Coronary Units The Spanish Society of Thrombosis and Hemostasia 'HEMOMAS' group **Author:** Llau et al.[16]	Multidisciplinary management of massive haemorrhage from diagnosis to management and control	A series of experts belonging to the 3 societies contributed the creation of the consensus document which included review of the literature and appraisal of the evidence base. Endorsed by the 3 societies.	Literature search of the Cochrane Library, Medline and Guiasalud databases **Search dates:** March 2013 searching previous 10 years	GRADE criteria as described by Guyatt et al.[24] **Strength of recommendation:** Grade 1: Strong recommendation Grade 2: Weak recommendation **Quality of evidence**: A: High quality B: Moderate quality C: Low quality D: Very low quality
US 2015 Originally published 2006	American Society of Anaesthesiologists (ASA) Task force on Perioperative Blood Management **Author:** Apfelbaum et al.[17]	Perioperative management of blood transfusion and adjuvant therapies across inpatient and outpatient surgical settings in which significant blood loss occurs or is expected	Seven-step process; Consensus on criteria for evidence, Expert panel consultation via surveys, Expert panel review and comment of draft, Survey of society members on recommendations, Open forums at national meetings for input, Survey of expert consultants of feasibility of implementation and use of all	Literature citations from PubMed and other healthcare databases, direct internet searches, Task Force members, liaisons with other organizations and manual searches of references in reviewed articles. **Search dates:** 2004 to 2014 combined with pre-	*Scientific evidence:* Category A: RCTs (Level 1= sufficient to meta-analyse, Level 2= multiple but no meta-analysis, Level 3= single study), designated as beneficial (B), harmful (H), or equivocal (E). Category B: Observational studies or RCTs without pertinent comparators (Level 1= observational comparisons, Level 2= observational studies with associative statistics, Level 3= non-comparative observational studies with descriptive statistics, Level 4=case reports), designated as either beneficial (B) or

Country Year	Associated society or body Primary author	Primary topic of guideline	Development Process	Details of evidence base Search dates	Certainty of evidence and strength of recommendations
			available information to build consensus within Task Force.	2005 articles used in the previous update Opinion surveys developed to address each clinical intervention identified in the document and distributed to expert consultants and a random sample of ASA members.	harmful (H) for the patient; statistically non-significant findings designated as equivocal (E) *Opinion-based evidence:* Category A: Expert Opinion. Survey responses from Task Force-appointed expert consultants. Category B: Membership Opinion. Survey responses from active ASA members.
Australia 2011 Currently being updated- expected completion 2020 Associated systematic review to update selective evidence in 2015 by McQuilten et al.[22] which did not affect the original recommendations	Australian National Blood Authority (ANBA) **Author:** Turner et al.[18]	Transfusion management of critical bleeding in all settings	Definition of research questions by Expert working group, Clinical reference group and Guideline assessment Register. Systematic review of literature. Formulation of recommendations and practice points based on evidence base and consensus. Approved by the National Health and Medical Research Council.	Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant, and literature recommended by expert members of the Clinical Reference Group. **Search dates:** Studies published before July 2009. McQuilten et al.[22] update up to 2014 which did not affect original recommendations.	The body of evidence was consolidated into evidence statements and rated according to a matrix, which considers 5 domains: evidence base, consistency, clinical impact, generalisability and applicability. Graded as per the guidance provided by the National Health and Medical Research Council: A: Body of evidence can be trusted to guide practice B: Body of evidence can be trusted to guide practice in most situations C: Body of evidence provides some support for recommendation(s) but care should be taken in its application D: Body of evidence is weak and recommendations must be applied with caution. Practice Points: Developed by Clinical Reference Group where no high-quality data was found to produce

Country **Year**	**Associated society or body** **Primary author**	**Primary topic of guideline**	**Development Process**	**Details of evidence base** **Search dates**	**Certainty of evidence and strength of recommendations**
					evidence-based recommendations, but group felt that clinicians required guidance to ensure good clinical practice.
Italy 2011	Italian Society of Transfusion Medicine and Immunohaematology (ISTMI) **Author:** Liumbruno et al.[19]	Transfusion management of patients in the intraoperative period	Recommendations developed in conformity with the indications in the methodological manual of the national programme for guidelines from the Istituto Superiore di Sanità (inaccessible)	Use of systematic literature reviews and updates of already existing recommendations on the subject. **Search dates:** Not provided	Grading recommendations described by Guyatt et al.[25]: 1A: Strong recommendation; Clear risk/benefit; RCTs without important limitations 1C+: Strong recommendation; Clear risk/benefit; No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies 1B: Intermediate-strength recommendation; Clear risk/benefit; RCTs with important limitations 1C: Intermediate-strength recommendation; Clear risk/benefit; Observational studies 2A: Intermediate-strength recommendation; Unclear risk/benefit; RCTs without important limitations 2C+: Weak recommendation; Unclear risk/benefit; No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies 2B: Weak recommendation; Unclear risk/benefit; RCTs with important limitations 2C: Very weak recommendation; Unclear risk/benefit; Observational studies

Country **Year**	**Associated society or body** **Primary author**	**Primary topic of guideline**	**Development Process**	**Details of evidence base** **Search dates**	**Certainty of evidence and strength of recommendations**
United Kingdom 2010	AAGBI **Author:** Thomas et al.[20]	Management of massive haemorrhage	Consensus document produced by expert members of a working party. Documents seen and approved by the council of the AAGBI	No information provided	No information provided
International 2009	World Health Organisation (WHO) **Author:** Gawande et al.[21]	Safety across all surgical care	International consultation meeting held. Expert working groups created to systematically review the available scientific evidence, write the guidelines document and facilitate discussion in order to formulate the recommendations. A steering group signed off on the content and recommendations. The guidelines were pilot tested in each of the 6 WHO regions.	Systematic review of evidence **Search dates:** Not provided	Potentially beneficial practices classified into 3 categories on the basis of clinical evidence or expert opinion as to their ability to reduce the likelihood of serious, avoidable surgical harm and whether adherence is unlikely to introduce injury or unmanageable cost: • Highly recommended: a practice that should be in place in every operation • Recommended: a practice that is encouraged for every operation • Suggested: a practice that should be considered for any operation
Ireland 2002	National Blood Users Group (NBUG) **Author:** Bonnar et al.[10]	In-hospital blood and blood component use in the management of massive haemorrhage	No information provided	No information provided	Grade A-(evidence levels Ia, Ib): At least one RCT as part of the body of literature of overall good quality and consistency addressing the specific recommendation. Grade B- (evidence levels IIa, IIb, III): Availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

Country **Year**	**Associated society or body** **Primary author**	**Primary topic of guideline**	**Development Process**	**Details of evidence base** **Search dates**	**Certainty of evidence and strength of recommendations**
					Grade C- (evidence level IV): Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

Key: GRADE- Grading of Recommendations, Assessment, Development and Evaluation; RCT- Randomised Controlled Trial

3.3 Currency of guidelines

The majority of recommendations extracted from the included guidelines were formulated on expert opinion, low quality evidence or lacked clarity in formulation. Thus, assessment of currency based on the dates of systematic literature searches is impractical and a narrative commentary on the year of publication of each guideline is instead provided.

Two guidelines were published since 2016 with the most recent produced by the AAGBI[14] in 2016 for the use of blood and blood components. The BCSH[15] guideline for the haematological management of major haemorrhage was first published in 2015 (based on literature up to April 2015), an addendum added in 2017 and a full update is currently planned with expected completion in 2021.

The ASA[17] guideline for perioperative blood management was most recently published in 2015 (with literature up to 2014) based on periodic updates on the original guideline developed in 2006. The HEMOMAS[16] guideline for massive haemorrhage management was produced in 2015 (based on literature from 2003 to 2013) with the ANBA systematic review update of evidence also published in 2015 with the aim of updating a portion of the evidence base for critical bleeding management from the original guideline published in 2011.[18, 22] The ANBA guideline is undergoing a full update which is scheduled for public consultation in 2020. The ISTMI[19] guideline for intraoperative blood loss was produced in 2011 and the AAGBI[20] guideline for massive blood loss in 2010.

The remaining two guidelines are over ten years old with the WHO[21] safe surgical guidelines published in 2009 and the oldest guideline within this review produced by the NBUG[10] in Ireland for the management of massive haemorrhage in 2002.

3.4 Definition or description of massive haemorrhage

A detailed overview of the definitions and descriptions of massive haemorrhage included by the guidelines within this review is provided in Table 3.2.

Three of the guidelines used the following three measures of blood loss to define massive haemorrhage,[14-16] with one additional guideline using these criteria but in terms of transfusion need rather than blood loss;[10]

1. Loss equivalent to one blood volume in a 24-hour period.
2. Loss equivalent to 50% of blood volume over a three-hour period.
3. Loss of blood volume at a rate of 150ml/minute.

The HEMOMAS and NBUG guidelines highlight that the third measure of blood loss at a rate

of 150ml/minute may be the most beneficial where loss is quantifiable.[10, 16] The ISTIMI guideline refers specifically to intraoperative blood loss and considers blood loss of 20% or more of blood volume to be major.[19]

Two guidelines describe a clinically-focused definition of bleeding which results in systolic blood pressure of less than 90mmHg and a heart rate of more than 110 beats per minute.[14, 15] A description of bleeding which is life-threatening in nature and requires massive transfusion was provided by two guidelines.[16, 18]

The ASA[17] and WHO[21] guidelines do not provide explicit definitions or descriptions of massive haemorrhage. However, the WHO guideline does highlight the American College of Surgeons Advanced Trauma Life Support manual classification of hypovolaemic shock associated with acute blood loss which includes quantified measures and associated clinical characteristics across four classes.[21] The WHO guideline further highlights that rapid blood loss can result in paradoxical bradycardia and that the absence of tachycardia does not reliably rule out significant blood loss.[21]

Table 3.2 Definition or description of massive haemorrhage within included guidelines

Guideline	Definition or description of massive haemorrhage
AAGBI 2016 **Author:** Klein et al.[14]	Describes the following definitions: • Loss of more than one blood volume within 24 hours • 50% of total blood volume lost in less than 3 hours • Bleeding in excess of 150 ml/min Describes a pragmatic clinically-based definition: • Bleeding which leads to a systolic blood pressure of less than 90 mmHg or a heart rate of more than 110 beats/min.
BCSH 2015 **Author:** Hunt et al.[15]	Describes the following definitions: • Loss of one blood volume within a 24 hour period • 50% blood volume loss within 3 hours • Loss of 150 ml/min Guideline definition: • Bleeding which leads to a heart rate more than 110 beats/min and/or systolic blood pressure less than 90 mmHg.
HEMOMAS 2015 **Author:** Llau et al.[16]	Describes the following definitions: • Blood loss of over 150 ml/min for more than 10 minutes • Loss of a blood volume in 24 hours • Requiring the transfusion of four red cell concentrate units in one hour • Loss of 1-1.5 volume equivalent in 24 hours • Loss of 50% of volume equivalent in 3 hours • Life-threatening major haemorrhage requiring massive transfusion. The panel of experts agreed that the first definition is probably the best when the blood losses are quantifiable.
ASA 2015 **Author:** Apfelbaum et al.[17]	No description provided

ANBA 2011 **Author:** Turner et al.[18]	Critical bleeding: Major haemorrhage that is life threatening and likely to result in the need for massive transfusion
ISTMI 2011 **Author:** Liumbrano et al.[19]	Specifically related to intra-operative major bleeding: • Loss of 20% or more of the volume of blood.
AAGBI 2010 **Author:** Thomas et al.[20]	The nature of the injury will usually alert the anaesthetist to the probability of massive haemorrhage and can be arbitrarily considered as a situation where 1–1.5 blood volumes may need to be infused either acutely or within a 24-hour period.
WHO 2009 **Author:** Gawande et al.[21]	A specific definition of massive haemorrhage was not provided however the authors present a classification for hypovolaemic shock using the American College of Surgeons Advanced Trauma Life Support Classification of hypovolaemic shock: **Class I:** Blood loss; <750ml**,** Percentage blood volume lost; 15%, Pulse rate; <100**,** Blood pressure; Normal **Class II:** Blood loss; 750-1500ml**,** Percentage blood volume lost; 15-30%**,** Pulse rate; >100**,** Blood pressure; Normal to decreased **Class III:** Blood loss; 1500-2000ml, Percentage blood volume lost; 30-40%**,** Pulse rate; >120**,** Blood pressure; Decreased **Class IV (immediately life-threatening):** Blood loss; >2000ml, Percentage blood volume lost; >40%**,** Pulse rate; >140**,** Blood pressure; Markedly decreased Authors highlight that massive rapid uncompensated blood loss can paradoxically result in relative bradycardia. In addition, the absence of tachycardia does not reliably rule out severe blood loss.
NBUG 2002 **Author:** Bonnar et al.[10]	Describes the following definitions: • An ongoing transfusion requirement in an adult of more than 150 ml per minute • Replacement of more than 50% of blood volume in 3 hours or less • Replacement of one blood volume, or transfusion of 10 units or more of red cells in a 24 hour period Authors highlight that ongoing blood loss of more than 150ml per minute has a benefit of allowing early recognition of major blood loss

3.5 Recommendations of interest

Four topics of interest for guideline recommendations were highlighted by the GDG; recognition of massive haemorrhage, organisational aspects of massive haemorrhage management, surgical management of massive management and audit of management of massive haemorrhage. A matrix of recommendations included by the guidelines is provided in Table 3.3, with a detailed overview of the recommendations in Table 3.4. The wording of recommendations has not been altered in any way from the original guidelines. In general, the recommendations presented are based on expert opinion or are unclear in their underlying basis.

3.5.1 Recommendations on recognition

Three guidelines included in this review had recommendations concerning the recognition of massive haemorrhage.[15, 17, 19]

The BCSH guideline on the haematological management of major haemorrhage recommends that any medical, nursing or midwifery staff working in frontline areas must be trained to recognise major blood loss, when to activate the local major haemorrhage protocol, and take prompt and appropriate action.[15] The ASA guideline on perioperative blood management recommends the use of quantitative measurement of intraoperative blood loss with periodic visual assessment of the surgical field including checking suction canisters, sponges and drains.[17] The ISTIMI highlight that haemoglobin and haematocrit values may remain normal when considering intraoperative blood loss until plasma volume is restored and therefore recommend that the clinical examination of the patient is important.[19]

3.5.2 Recommendations on organisational aspects

Recommendations regarding organisational aspects included the use of protocols, the training of staff, communication and logistic considerations. Eight guidelines had recommendations considered to be relevant.[10, 14-18, 20, 21]

Seven of the guidelines recommended hospitals having local protocols in place for major haemorrhage or massive transfusion,[10, 14-18, 20]with further specifications made around adaptations for clinical areas,[15] coordination on a multidisciplinary basis,[16] the use of an alarm system[16] and inclusion of clinical, laboratory and logistic responses.[20] One guideline provided a template for the development of such protocols.[18]

Knowledge of and training in these protocols for staff was recommended by three guidelines.[10, 15, 16] Two guidelines made recommendations regarding communication when a

major haemorrhage or transfusion protocol is activated,[10, 15] with the need for a clear mechanism to be in place for contacting all relevant team members[15] and ensuring the relevant laboratories are aware of the activation.[10] The appointment of a team leader who should coordinate communication with relevant staff and overall management upon activation of a major haemorrhage protocol was recommended by one guideline.[15]

Strategies to ensure the immediate availability of blood products, specifically Group O negative red blood cells, during life-threatening bleeding were recommended by two guidelines, with further consideration of strategies for the timely provision of group specific red blood cells by the transfusion laboratory.[14, 15] One guideline recommended the availability of locally developed shock packs in hospitals where the mangement of massive haemorrhage is frequent.[20]

With regards to surgical blood loss the WHO guideline on safe surgery recommends that before inducing anaesthesia the anathestist should consider if large volume blood loss is a significant risk and should prepare appropriately, highlighting the potential of occurrence with the surgeon if the risk is unknown.[21] Prior to skin incision, approptiate intravenous access should be established if the risk of blood loss is significant, alongside a confirmation of blood product availability. This guideline also recommends communication prior to skin incision with the surgeon ensuring that the team is aware of the risk of heavy blood loss, and any other relevant safety concerns.[21]

3.5.3 Recommendations on surgical management

Recommendations considered potentially relevant to the surgical management of massive haemorrhage were presented in three guidelines.[10, 16, 20] Two guidelines recommended the timely control of bleeding by surgical means,[10, 16] one was limited to a broad statement as opposed to specified surgical care,[10] while the HEMOMAS guideline recommended the use of angioembolization or endovascular techniques for the treatment of massive haemorrhage in selected patient groups.[16] The 2010 AAGBI guideline for massive blood loss recommends that the immediate control of obvious bleeding is of paramount importance through the application of pressure, tourniquets or haemostatic dressings.[20]

3.5.4 Recommendations on audit

Three guidelines provided recommendations regarding the audit of management of massive haemorrhage.[14-16] Two guidelines referred to regular auditing and review of massive transfusion protocols, with an assessment of efficacy and safety,[14, 16] and one recommended multidisciplinary audit and case review to ensure effective systems are in place for major haemorrhage management.[15]

Table 3.3 Matrix of recommendations of interest

	AAGBI 2016[14]	BCSH 2015[15]	HEMOMAS 2015[16]	ASA 2015[17]	ANBA 2011[18]	ISTMI 2011[19]	AAGBI 2010[20]	WHO 2009[21]	NBUG 2002[10]
Recognition									
Training of staff		✓							
Physiological indications						✓			
Surgical visual monitoring				✓					
Organisational aspects									
Major haemorrhage or transfusion protocol	✓	✓	✓	✓	✓		✓		✓
Knowledge of/ training in protocols		✓	✓						✓
Communication when protocol activated		✓							✓
Communication in surgery to prevent blood loss								✓	
Team leader appointed when protocol activated		✓							
Availability of blood products	✓	✓						✓	
Use of shock packs							✓		
Surgical Management									
Timely control of bleeding							✓		✓
Angioembolization or endovascular management			✓						
Audit									
Major haemorrhage protocol		✓							
Massive transfusion protocols	✓		✓						

Table 3.4 Overview of recommendations of interest included by guidelines

Associated society or body Author	Recommendations on recognition	Recommendations on organisational aspects	Recommendations on surgical management	Recommendations on audit of management
AAGBI 2016 **Author:** Klein et al.[14]	No recommendations included	Every institution should have a massive transfusion protocol which is regularly audited and reviewed. **Strength of recommendation:** Not reported Group O red cells for transfusion should be readily available in the clinical area, in case haemorrhage is life-threatening. Group-specific red cells should be available within a very short time (15–20 min) of the laboratory receiving correctly-labelled samples and being informed of the emergency requirement for blood. **Strength of recommendation:** Not reported	No recommendations included	Every institution should have a massive transfusion protocol which is regularly audited and reviewed. **Strength of recommendation:** Not reported
BCSH 2015 **Author:** Hunt et al.[15]	Medical, nursing and midwifery staff involved in frontline care must be trained to recognize major blood loss early, know when to activate/trigger the local major haemorrhage protocol and take prompt and appropriate action. **Strength of recommendation:** Grade 1D (Strong recommendation, expert opinion)	Hospitals must have local major haemorrhage protocols with adaptations for specific clinical areas. **Strength of recommendation:** Grade 1D (Strong recommendation, expert opinion) All medical, nursing, laboratory and support staff must know where to find the haemorrhage protocol in relevant areas and be familiar with the contents; their knowledge should be supported by training and regular drills. **Strength of recommendation:** Grade 1D(Strong recommendation, expert opinion) Following trigger of the major haemorrhage protocol there must be a clear mechanism for contacting all relevant team	No recommendations included	Multidisciplinary audit and case review should be undertaken to ensure that effective systems are in place for major haemorrhage management. **Strength of recommendation:** Grade 1A (Strong recommendation, high quality evidence)

Associated society or body Author	Recommendations on recognition	Recommendations on organisational aspects	Recommendations on surgical management	Recommendations on audit of management
		members and a designated Team Leader should then coordinate further management. **Strength of recommendation:** Grade 1D (Strong recommendation, expert opinion) A Team Leader should be appointed and nominate a specific clinical team member to co-ordinate communication with Transfusion Laboratory staff and support services for the duration of the incident. **Strength of recommendation:** Grade 1D (Strong recommendation, expert opinion) Hospitals must have a strategy to ensure that red cells are readily available for life-threatening bleeding, through the use of emergency Group O red cells and also through the rapid provision of group-specific red cells by the transfusion laboratory. **Strength of recommendation:** Grade 1C (Strong recommendation, low quality evidence)		
HEMOMAS 2015 **Author:** Llau et al.[16]	No recommendations included	Institutions should develop massive transfusion protocols coordinated on a multidisciplinary basis, with management algorithms fundamented upon scientific evidence. Likewise, informative and training campaigns are recommended, targeted to the teams involved, with periodic evaluation of compliance and effectiveness and compliance. **Strength of recommendation:** C (Low quality evidence)	The evaluation of measures without transfusion, such as angioembolization or the use of endovascular procedures, is recommended for the treatment of massive hemorrhage in selected	Transfusion protocols in massive haemorrhage should function with an alarm system defined by the hemotherapy commission of each individual hospital, as a consensus-based interdisciplinary protocol, with period assessment of its efficacy and safety.

Associated society or body **Author**	**Recommendations on recognition**	**Recommendations on organisational aspects**	**Recommendations on surgical management**	**Recommendations on audit of management**
			patients, provided such measures are available. **Strength of recommendation:** 1B (Strong recommendation, moderate quality evidence)	**Strength of recommendation:** 2C (Weak recommendation, low quality evidence)
ASA 2015 **Author:** Apfelbaum et al.[17]	Use standard methods for quantitative measurement with periodic visual assessment of blood loss, including checking suction canisters, surgical sponges, and surgical drains. **Strength of recommendation:** *Scientific evidence:* Insufficient literature. *Opinion-based:* Category A and B strongly agree with recommendation	A massive (i.e. haemorrhagic) transfusion protocol may be used when available as a strategy to optimize the delivery of blood products to massively bleeding patients. **Strength of recommendation:** *Scientific Evidence:* Category B3-E (non-comparative observational studies with descriptive statistics, statistically non-significant findings) *Opinion-based:* Category A and B strongly agree with recommendation	No recommendations included	No recommendations included
ANBA 2011 **Author:** Turner et al.[18]	No recommendations included	In critically bleeding patients requiring, or anticipated to require, massive transfusion, an MTP should be used. **Strength of recommendation:** Practice point	No recommendations included	No recommendations included
ISTMI 2011 **Author:** Liumbruno et al.[19]	Patients with acute haemorrhage can have normal, or even raised, values of Htc and Hb until the plasma volume is restored; in these cases,	No recommendations included	No recommendations included	No recommendations included

Associated society or body **Author**	**Recommendations on recognition**	**Recommendations on organisational aspects**	**Recommendations on surgical management**	**Recommendations on audit of management**
	therefore, the clinical examination of the patient becomes extremely important **Strength of recommendation:** Grade 2C+ (Very weak recommendation, low quality evidence)			
AAGBI 2010 **Author:** Thomas et al.[20]	No recommendations included	Hospitals must have a major haemorrhage protocol in place and this should include clinical, laboratory and logistic responses. **Strength of recommendation:** Not reported The major haemorrhage protocol must be mobilised immediately when a massive haemorrhage situation is declared. **Strength of recommendation:** Not reported In hospitals where the need to treat massive haemorrhage is frequent, the use of locally developed shock packs may be helpful. **Strength of recommendation:** Not reported	Immediate control of obvious bleeding is of paramount importance (pressure, tourniquet, haemostatic dressings) **Strength of recommendation:** Not reported	No recommendations included
WHO 2009 **Author:** Gawande et al.[21]	No recommendations included	Before inducing anaesthesia, the anaesthetist should consider the possibility of large-volume blood loss, and, if it is a significant risk, should prepare appropriately. If the risk is unknown, the anaesthetist should communicate with the surgeon regarding its potential occurrence.	No recommendations included	No recommendations included

Associated society or body Author	Recommendations on recognition	Recommendations on organisational aspects	Recommendations on surgical management	Recommendations on audit of management
		Strength of recommendation: Highly recommended (a practice that should be in place in every operation) Before skin incision, the team should discuss the risk for large-volume blood loss and, if it is significant, ensure that appropriate intravenous access is established. **Strength of recommendation:** Highly recommended (A practice that should be in place in every operation) A member of the team should confirm the availability of blood products if needed for the operation. **Strength of recommendation:** Recommended (A practice that is encouraged for every operation) Before skin incision, the surgeon should ensure that team members, in particular nurses, anaesthetists, and surgical assistants are aware of the critical steps of the procedure to be performed, the risk for heavy blood loss, any special equipment needed (such as instruments, implants, intraoperative imaging, frozen section pathology) and any likely deviation from routine practice. The nurse(s) should inform the team members about any critical safety concerns and then lack of availability or preparation of any special equipment. The anaesthetist should inform the team about any critical safety concerns, in particular any difficulty in preparing for resuscitation after heavy blood loss or patient comorbidities that add risk to the anaesthesia.		

Associated society or body **Author**	**Recommendations on recognition**	**Recommendations on organisational aspects**	**Recommendations on surgical management**	**Recommendations on audit of management**
		Strength of recommendation: Highly recommended (A practice that should be in place in every operation)		
NBUG 2002 **Author:** Bonnar et al.[10]	No recommendations included	**<u>General recommendations</u>** Perform interventions according to a planned protocol, and in parallel as appropriate. **Strength of recommendation:** Not reported Send for senior help early. **Strength of recommendation:** Not reported Make sure that the relevant laboratories are aware that a massive haemorrhage is in progress. **<u>Specific recommendations</u>** **Strength of recommendation:** Not reported Know and implement the specific local procedures for dealing with the logistic demands of massive transfusion. **Strength of recommendation:** Not reported	Control the source of haemorrhage, surgical or radiological, should be implemented immediately. Patients should be transferred urgently to an area where definitive intervention for diagnosis and treatment can occur. **Strength of recommendation:** Not reported	No recommendations included

3.6 Quality appraisal

An overview of the methodological quality of the included guidelines, as assessed by the AGREE-II tool, is provided in Table 3.5 and summarised below. The scaled domain scores are presented for each guideline in accordance with the AGREE-II manual.[13] The included guidelines varied in terms of quality with no guideline found to be of consistently high quality across all six domains.

Domain 1: Scope and Purpose

The BCSH[15] and WHO[21] guidelines possessed the highest scores (78%) in terms of describing the scope and purpose of their respective guidelines. The remaining guidelines did not provide full descriptions of the objectives, health questions or relevant populations.

Domain 2: Stakeholder Involvement

The guidelines produced by the BSCH,[15] ASA,[17] ANBA[18] and WHO[21] (all >60%) achieved the highest scores with regards to stakeholder involvement. A lack of description of the relevant audience to whom each of the guidelines was intended to apply and how the recommendations were intended to be used led to the remaining guidelines receiving lower scores in this domain.

Domain 3: Rigour of Development

With the exceptions of the BCSH[15] guideline for the haematological management of major haemorrhage (61%) and ANBA[18] guideline for critical bleeding (73%), the guidelines consistently achieved low scores in terms of rigour of development. Areas of poor reporting were widespread within the domain with poorly described or a complete absence of a clear evidence base and methods for formulating recommendations.

Domain 4: Clarity of Presentation

The clarity of presentation domain had the most consistently high scores across the included guidelines, with seven of the nine included scoring above 60%. The majority provided recommendations that were easily identifiable, clearly articulated and frequently considered different management options for the topics of interest within the guideline.

Domain 5: Applicability

The majority of the included guidelines had low scores in terms of adequate consideration of applicability, with the exception of the WHO[21] and ANBA guidelines.[18] The guidelines did not sufficiently consider the barriers and facilitators, resource implications, implementation and audit criteria for their respective guideline.

Domain 6: Editorial Independence

Adequate reporting of funding and conflicts of interest was highly variable. The HEMOMAS[16] and ANBA[18] guidelines largely fulfilled the criteria in terms of editorial independence, with the remaining guidelines partially reporting these criteria, reporting one aspect or not reporting either.

Table 3.5 Quality of included guidelines by the AGREE-II tool domains

Guideline	**Domain 1** Scope and Purpose	**Domain 2** Stakeholder Involvement	**Domain 3** Rigour of Development	**Domain 4** Clarity of Presentation	**Domain 5** Applicability	**Domain 6** Editorial Independence
AAGBI 2016[14]	53%	11%	3%	75%	2%	75%
BCSH 2015[15]	78%	64%	61%	81%	31%	71%
HEMOMAS 2015[16]	47%	36%	31%	64%	6%	100%
ASA 2015[17]	67%	67%	42%	64%	15%	50%
ANBA 2011[18]	64%	61%	73%	72%	56%	96%
ISTMI 2011[19]	28%	19%	21%	64%	0%	0%
AAGBI 2010[20]	39%	11%	10%	56%	0%	0%
WHO 2009[21]	78%	67%	33%	78%	65%	50%
NBUG 2002[10]	56%	50%	9%	36%	4%	0%

4 Discussion

Nine guidelines, which possessed one or more recommendations on the specific topics of interest to the Unexpected Intraoperative Life Threatening Haemorrhage GDG, were evaluated in this review.[10, 14-21] The included guidelines predominantly focused on the transfusion or haematological management of bleeding or massive haemorrhage, with no guidelines identified providing specific guidance on intraoperative massive haemorrhage as the primary topic. Recommendations relating to the organisational aspects of massive haemorrhage management were present in eight of the nine included guidelines. Recommendations were limited in terms of recognition, surgical management and audit of management for massive haemorrhage. The overall quality of the included guidelines was varied with no guideline being of consistently high quality across all assessed domains, and the majority of recommendations of interest based on expert opinion or lacking clarity in their formulation.

In terms of the definition or description of massive haemorrhage utilised by the included guidelines, three quantifiable measures of blood loss were consistently used;

1. Loss equivalent one blood volume in a 24-hour period.
2. Loss equivalent to 50% of blood volume over a three-hour period.
3. Loss of blood volume at a rate of 150ml/minute.

However, the included guidelines frequently highlighted these definitions as being arbitrary, retrospective and of limited use in the acute setting where the degree of blood loss is unlikely to be quantifiable. A clinically-focused definition of a reduction in systolic blood pressure (less than 90mmHg) and an increase in heart rate (greater than 110 beats per minute) was highlighted as a potentially more pragmatic indication of massive haemorrhage by two of the included guidelines. However, the WHO guideline urges caution when relying on raised heart rate (tachycardia) to identify blood loss as it is a potentially misleading indicator.[21] Tachycardia is a cardiovascular response to bleeding in an effort to maintain cardiac output, however acute haemorrhage can result in an initial absence of tachycardia where the heart rate remains normal or even reduced; this phenomenon has been termed relative bradycardia, absence of tachycardic response or paradoxical bradycardia, and has been observed in trauma and non-trauma populations.[26] In December 2019, an audit of practice in Ireland was undertaken by the Unexpected Intraoperative Life Threatening Haemorrhage GDG including 45 hospital based blood banks and two distribution centres. Preliminary results of this audit indicated that of hospitals who utilised a blood loss metric to define massive haemorrhage 16/34 used blood loss at a rate of 150ml/minute, and of those including a cardiovascular indicator 8/15 used the definition of heart rate above 110 beats per minute and systolic blood pressure of less than 90mmHg.

The difficulties in pragmatically defining massive haemorrhage were further seen in recommendations relating to recognition where the included guidelines offered little in terms of clinical guidance but rather emphasised the necessity of early recognition and training of staff to enable timely management. This aspect was further highlighted by two guidelines within this review although not as formal recommendations.[14, 18] Given that the timely recognition and initiation of management are crucial to the morbidity and mortality outcomes of a patient experiencing massive haemorrhage, appropriate indicators to facilitate this recognition are crucial.[27] In trauma populations, a large number of tools and algorithms exist to assist clinicians in recognising massive haemorrhage and in decision-making for management such as the Assessment of Blood Consumption score, the Trauma-Associated Severe Haemorrhage score and the Traumatic Bleeding Severity Score.[28] However, there is lack of such prediction tools and models when considering massive haemorrhage and the need to activate massive haemorrhage protocols in non-trauma populations.[27, 29]

With regards to organisational aspects of massive haemorrhage management there was consistency among the guidelines regarding the use of massive haemorrhage and massive transfusion protocols. The two terms are largely interchangeable with 'massive haemorrhage protocol' reflecting more modern terminology where patients are not defined by transfusion need.[30, 31] The recommendations included elements such as the creation and implementation of such protocols, communication pathways and multidisciplinary involvement. These recommendations appear paramount to the timely organisation of massive haemorrhage management whereby a protocol-driven multidisciplinary team approach is underpinned by clear lines of communication between all relevant hospital staff members.[3] The goal of massive haemorrhage protocols is to standardise care, improve communication and optimise the speed of blood product delivery.[30] Although standard practice in trauma centres, the adoption of massive haemorrhage protocols across hospital care is less certain with a recent survey of hospitals in Ontario in 2017 finding that one third did not have a massive haemorrhage protocol in place.[31] The audit of practice in Ireland undertaken by the Unexpected Intraoperative Life Threatening Haemorrhage GDG highlighted that 10 of the included hospitals do not currently have a massive haemororrhage protocol in place.

Further recommendations pertained to logistic responses such as the immediate availability of Group O red blood cells and the timely availability of group specific red-blood cells. Such organisational aspects are key to the timely management of massive haemorrhage with regards to transfusion,[3] with a haemovigilance reporting scheme in the United Kingdom highlighting that delays in the provision of blood products during emergency situations play a significant role in avoidable patient mortality.[32] Further organisational recommendations included clear communication between staff before and during surgical procedures for adequate preparation for potential blood loss as identified within the WHO safe surgery

guidelines.[21] Such features of safe surgical care have received growing attention in the pursuit of improving patient safety and surgical outcomes.[33]

Recommendations relating to the surgical management of massive haemorrhage were limited. The timely control of bleeding was highlighted as imperative to controlling a massive haemorrhage. Although not formally recommended, the definitive and timely surgical or interventional radiological control of bleeding was further cited by a number of guidelines within this review.[14, 15, 18] Norfolk[3] highlights that surgical control of bleeding must be coordinated with haematological involvement to ensure the effective management of massive haemorrhage overall. Intuitively, the nature of the surgical management of massive haemorrhage will be dictated by the nature of the cause.[1]

For the audit of management of massive haemorrhage, the recommendations in the guidelines included within this review primarily related to the audit of major haemorrhage and massive transfusion protocols with regular, multidisciplinary audits and case reviews recommended. Audits serve as quality assurance mechanisms when considering such protocols with the goal of enabling assessment of effect and compliance, and of identifying training opportunities and the need to review protocol content.[30]

The results of this review should be interpreted with consideration of a number of limitations. As the review question concerned the identification of clinical guidelines which are typically not included within electronic databases, an extensive grey literature search was required. A truly comprehensive search of the grey literature is difficult. However, as highlighted in Appendix 2, a considerable effort was made to include a diversity of sources in addition to electronic searches. Furthermore, the topic of interest to the GDG was intraoperative massive haemorrhage. As anticipated there was a dearth of guidelines relating explicitly to this topic and therefore the scope of the review included potentially transferable guidelines, and thus the recommendations extracted may not be directly related to intraoperative care.

4.1 Conclusions

Relevant recommendations were extracted from nine guidelines within this review. No guideline was identified which addressed the management of intraoperative massive haemorrhage as the primary topic, with the majority of guidelines concerned with the transfusion or haematological management of bleeding, or massive haemorrhage explicitly. The methodological quality of the included guidelines was varied with particular deficits evident in the rigour of development of the included guidelines, and the majority of recommendations of interest based on expert opinion or lacking clarity in their origins. Some consistency existed with regards to the definition or description of massive haemorrhage, however there were criticisms of these definitions as being arbitrary and retrospective with limited clinical practicality. Eight of the nine included guidelines made recommendations with regards to organisational aspects of massive haemorrhage management, while

recommendations considered relevant to surgical management and audit of management were presented within three guidelines for each respective topic of interest.

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Appendix 1: Electronic database search terms and search results

PubMed 26 September 2019		**Results =1055**
1.	haemorrhage[Title/Abstract]	34089
2.	hemorrhage[Title/Abstract]	146245
3.	bleeding[Title/Abstract]	191835
4.	blood-loss[Title/Abstract]	49061
5.	exsanguinati*[Title/Abstract]	2454
6.	"vessel injury"[Title/Abstract]	1323
7.	"vascular injury"[Title/Abstract]	10272
8.	bleeding[MeSH Terms]	319699
9.	surgical hemorrhage[MeSH Terms]	17053
10.	exsanguinating hemorrhage[MeSH Terms]	334
11.	hemorrhagic shock[MeSH Terms]	11257
12.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	545036
13.	Massive*	100012
14.	Major*	1754625
15.	Excessive*	127462
16.	Severe*	988088
17.	Catastrophic*	15625
18.	Critical*	901459
19.	Profound*	103683
20.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	3658614
21.	Guideline*[Title]	73563
22.	Recommendation*[Title]	36151
23.	Consensus[Title]	22889
24.	Guidance[Title]	16133
25.	Guideline[Publication type]	32595
26.	Practice guideline[publication type]	25751
27.	#21 OR #22 OR #23 OR #24 OR #25 OR #26	155603
28.	#12 AND #20 AND #27	1055
	Total	**1055**

Embase 26 September 2019		**Results = 2299**
1.	Haemorrhage:ab,ti	48576
2.	hemorrhage:ab,ti	185863
3.	bleeding:ab,ti	303877
4.	'blood loss':ab,ti	78220
5.	exsanguinati*:ab,ti	3569
6.	'vessel injury':ab,ti	1945
7.	'vascular injury':ab,ti	14078
8.	Bleeding/de	284692
9.	'operative blood loss'/de	20537
10.	Exsanguination/de	950
11.	'hemorrhagic shock'/de	17040
12.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	675530
13.	Massive*	129586
14.	Major*	5580946
15.	Excessive*	172896
16.	Severe*	1419788
17.	Catastrophic*	20014
18.	Critical*	1263338
19.	Profound*	134078
20.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	7836179
21.	Guideline*:ti	96644
22.	Recommendation*:ti	46101
23.	Consensus:ti	27421
24.	Guidance:ti	20374
25.	'Practice guideline'/mj	67718
26.	#21 OR #22 OR #23 OR #24 OR #25	208614
27.	#12 AND #20 AND #26	2299
	Total	**2299**

The Cochrane Library 27 September 2019		**Results = 115**
1.	("hemorrhage"):ti,ab,kw	4385
2.	(haemorrhage):ti,ab,kw	27621
3.	(bleeding):ti,ab,kw	40466
4.	('blood loss'):ti,ab,kw	27395
5.	(exsanguinat*):ti,ab,kw	122
6.	('vessel injury'):ti,ab,kw	918
7.	('vascular injury'):ti,ab,kw	2381
8.	MeSH descriptor: [Hemorrhage] explode all trees	13294
9.	MeSH descriptor: [Blood Loss, Surgical] explode all trees	2478
10.	MeSH descriptor: [Exsanguination] explode all trees	16
11.	MeSH descriptor: [Shock, Hemorrhagic] explode all trees	92
12.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	80558
13.	Massive*	1926
14.	Major*	291576
15.	Excessive*	9471
16.	Severe*	106367
17.	Catastrophic*	499
18.	Critical*	44504
19.	Profound*	4047
20.	#13 OR #14 OR #15 OR #16 OR #18 OR #19	332728
21.	(guideline*):ti	2593
22.	(recommendation*):ti	1087
23.	(consensus):ti	461
24.	(guidance):ti	1109
25.	(guideline):pt	33
26.	(practice guideline):pt	23
27.	#21 OR #22 OR #23 OR #24 OR #25 OR #26	5134
28.	#12 AND #20 AND #27	115
	Total	**115**

CINAHL 26 September 2019		**Results = 595**
1.	TI haemorrhage OR AB haemorrhage	25548
2.	TI hemorrhage OR AB hemorrhage	28337
3.	TI bleeding OR AB bleeding	34154
4.	TI "blood loss" OR AB "blood loss"	9614
5.	TI exsanguinat* OR AB exsanguinat*	409
6.	TI "vessel injury" OR AB "vessel injury"	207
7.	TI "vascular injury" OR AB "vascular injury"	1294
8.	MH hemorrhage+	55405
9.	MH surgical blood loss	280
10.	MH shock, hemorrhagic	1646
11.	(MM "Hemostasis, Surgical")	554
12.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	94201
13.	Massive*	10453
14.	Major*	254328
15.	Excessive*	21128
16.	Severe*	170453
17.	Catastrophic*	4088
18.	Critical*	182087
19.	Profound*	14103
20.	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	604192
21.	TI guideline*	38727
22.	TI recommendation*	16014
23.	TI guidance*	8468
24.	TI consensus*	7448
25.	MH practice guidelines	69528
26.	S21 OR S22 OR S23 OR S24 OR S25	113705
27.	S12 AND S20 AND S26	595
	Total	**595**

Appendix 2: Grey literature search and GDG consultation results

Guideline sources	Date searched	Documents added to screening
Department of Health	25 September 2019	2
Health Service Executive (HSE)	25 September 2019	4
Lenus	25 September 2019	5
National Institute for Health and Care Excellence (NICE)	25 September 2019	2
Guidelines and Audit Implementation Network / The Regulation and Quality Improvement Authority	25 September 2019	2
Scottish Intercollegiate Guidelines Network (SIGN)	25 September 2019	1
Guidelines International Network (GIN)	27 September 2019	9
Guideline Central	27 September 2019	3
Institute for Clinical Systems Improvement (ICSI)	27 September 2019	1
Emergency Care Research Institute (ECRI) Guidelines Trust	27 September 2019	0
New Zealand Guidelines Group	27 September 2019	0
Canadian Agency for Drugs and Technology in Health	27 September 2019	2
Haute Autorité de santé (HAS)	27 September 2019	1
Ontario Guidelines Advisory Committee (GAC) Recommended Clinical Practice Guidelines	27 September 2019	0
Finnish Medical Society Duodecim	1 October 2019	0
World Health Organisation	1 October 2019	3
Australian National Health and Medical Research Council Clinical Practice	1 October 2019	0
Canadian Medical Association InfoBase	1 October 2019	4
Institute for Healthcare Improvement (IHI)	1 October 2019	0

Japan Council for Quality Health Care	1 October 2019	1 (irretrievable)
Danish Health Authority – National Clinical Guidelines	27 September 2019	Inaccessible as website under construction
Singapore Ministry of Health	1 October 2019	1
Socialstyrelsen (Health and Medical Care and Social Services, Sweden)	1 October 2019	1
Geneva Foundation for Medical Education and Research	1 October 2019	14
Belgian Health Care Knowledge Centre	1 October 2019	0
AETSA (Andalusian Agency for Health Technology Assessment)	1 October 2019	0
German Institute of Medical Documentation and Information	1 October 2019	0

Professional Body Sources	**Date Searched**	**Documents added to screening**
Ireland		
Royal College of Physicians Ireland	2 October 2019	0
Irish Blood Transfusion Service	2 October 2019	3
United Kingdom		
British Society for Haematology	2 October 2019	4
The Association of Anaesthetists	2 October 2019	2
Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee	2 October 2019	1
European		
The European Hematology Association	2 October 2019	0
European Society of Anaesthesiology	2 October 2019	1
North America and Canada		
American Society of Anaesthesiologists	2 October 2019	1
American Society of Hematology	2 October 2019	0

Canadian Anaesthesiologists' Society	2 October 2019	0
Australia and New Zealand		
Australia and New Zealand Society for Blood Transfusion	2 October 2019	3
Australian and New Zealand college of Anaesthetists	2 October 2019	2
Other		
Network for the advancement of Patient Blood Management, Haemostasis and Thrombosis	2 October 2019	0

Additional sources	Date	Documents added to screening
GDG Consultation	4 to 25 September 2019	16

Appendix 3: Excluded citations following full-text review

Reason for exclusion	References
Does not possess recommendations of interest (n = 19)	(34-52)
Not a guideline (n = 17)	(1, 27, 29, 53-66)
Non-English with no available translation (n = 8)	(67-74)
Adapted or utilises other guideline recommendations (n = 4)	(75-78)
Conference abstract (n = 4)	(79-82)
Refers to specific procedure, technique or clinical population (n = 3)	(83-85)
Archived or superseded by an updated guideline (n = 3)	(86-88)
Does not refer to massive (or synonym) haemorrhage (n = 2)	(89, 90)
Local level guideline (n = 1)	(91)

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