

Appendix A- Full Guideline Methodology

Work Group Selection Process

This guideline is a joint effort of the American Society of Plastic Surgeons (ASPS), the American Society for Dermatologic Surgery (ASDS), the American Academy of Dermatology (AAD), the American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS), the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF), the American College of Mohs Surgery (ACMS), the American Society for Mohs Surgery (ASMS), and the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). ASPS and ASDS each provided a co-chair to coordinate the process.

All stakeholder organizations were invited to nominate members from their respective organizations to serve on the work group, following their own policies and procedures for addressing content expertise, guideline experience, and potential conflicts of interest. Four patient representatives were included on the panel to provide insight related to patient values and preferences. An ASPS quality department staff member was assigned to manage the project and provide expertise in clinical practice guideline development methodology. ASDS also provided staff support to the project.

All applicants were required to submit an online conflict of interest disclosure form for membership consideration. The co-chairs were free of all conflicts of interest for the duration of the project, as required by policy.

Clinical Question Development

Work group members used a consensus-based approach to select the clinical questions to be addressed in this evidence-based guideline. Clinical questions were submitted via a blinded process to the ASPS project manager, who compiled and dispersed the clinical questions for consideration and discussion at the introductory meeting. The clinical question topics were then discussed in detail at the in-person

introductory meeting with diverse representation from plastic surgery, dermatology, patients, and other specialties.

A total of 67 clinical questions were reviewed by the work group. Clinical questions were developed and selected based on the scope and importance to patient outcomes, as determined by the work group. The patient population for the guideline is adult patients who are being seen at the time of reconstruction, under the assumption that margins are clear of tumor. Patient-related outcomes of interest were determined to be infection rate, other surgical complications (e.g., hematoma, etc.), adverse events, risk of stroke or pulmonary embolism (specific to anticoagulation), pain, healing, and patient satisfaction. Final voting was completed by the work group via email following the meeting, which resulted in the following 7 clinical questions:

- 1) In adult patients undergoing reconstruction after skin cancer resection, does remaining on anticoagulants during surgery compared to stopping or bridging anticoagulants prior to surgery differ in the risks of stroke or pulmonary embolism, or surgical complications? (*corresponds to Recommendation 4*)
- 2) In adult patients undergoing reconstruction after skin cancer resection, does same day reconstruction compared to delayed reconstruction differ in infection rates, other complications, and patient satisfaction? (*corresponds to Recommendations 1 and 2*)
- 3) In adult patients undergoing reconstruction after skin cancer resection, does an administered perioperative systemic antibiotic regimen compared to none differ in infection rates, other complications, and patient satisfaction? (*corresponds to Recommendations 3*)
- 4) In adult patients undergoing reconstruction after skin cancer resection, does narcotics versus OTC medication use differ in measurement of pain and/or satisfaction with pain management? (*corresponds to Recommendation 5*)

- 5) In adult patients undergoing reconstruction after skin cancer resection, are there circumstances (anatomic location, defect size and/or depth, patient factors) when reconstruction should be performed the same day or delayed to affect aesthetic or functional outcomes, surgical complications, and patient satisfaction? *(corresponds to Recommendation 1)*
- 6) In adult patients undergoing delayed reconstruction after skin cancer resection, does a systemic antibiotic regimen administered during the interim between resection and reconstruction compared to none differ in infection rates, other complications, and patient satisfaction? *(corresponds to Recommendation 2)*
- 7) In adult patients undergoing reconstruction after skin cancer resection, does betadine versus chlorhexidine versus chloroxylonol versus ivory soap differ in infection rates or adverse events? *(did not result in a recommendation)*

Literature Search

Multiple literature searches were performed between 2017 and 2018 to identify relevant studies published from 1990 to 2018. The initial search dates were January 1, 1990 through March 12, 2018, with a subsequent update search on May 8, 2018. Electronic searches of PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were performed using appropriate combinations of the following MEDLINE Medical Subject Headings (MeSH) terms and keywords, as permitted by the search functionalities of each database/journal:

- **MeSH terms (used in PubMed only):** "Skin Neoplasms"[Mesh], "Carcinoma, Basal Cell"[Mesh], "Carcinoma, Squamous Cell"[Mesh], "Nevi and Melanomas"[Mesh], "Carcinoma, Merkel Cell"[Mesh], "Facial Neoplasms"[Mesh], "Lip Neoplasms"[Mesh], "Ear Neoplasms"[Mesh], "Nose Neoplasms"[Mesh], "Skull Base Neoplasms"[Mesh], "Dermatologic Surgical Procedures"[Mesh], "Mohs Surgery"[Mesh], "Surgery, Plastic"[Mesh], "Skin Transplantation"[Mesh], "Surgical Flaps"[Mesh]

- **Keywords:** skin cancer, reconstruction, skin graft, excision, resection, anticoagulants, fibrinolytic agents, antithrombotics, antiplatelets, platelet aggregation inhibitors, heparin, enoxaparin, lovenox, plavix, coumadin, warfarin, fragmin, dalteparin, innohep. tinzaparin, arixtra, fondaparinux, factor Xa inhibitor, angiomax, bivalirudin, refludan, aspirin, lepirudin, iprivask, desirudin, pradaxa, dabigatran etexilate, xarelto, rivaroxaban, apixaban, time-to-treatment, same-day, delayed, surgery, procedure, timing of surgery, anti-bacterial agents, antibiotic prophylaxis, narcotics, opioid, anti-inflammatory agents, non-steroidal, NSAID, naproxen, acetaminophen, analgesics, non-narcotic, pain management, postoperative pain, anti-infective agents, povidone-iodine, betadine, wokadine, pyodine, iodopovidone, chlorhexidine, chloroxylenol, PCMX, dettol, soaps, disinfectants, thrombocyte aggregation inhibition, blood clotting factor 10a inhibitor, thromboprophylaxis, clopidogrel, antibiotic therapy, anti-infective agent, opiate, opium, paracetamol, codeine, ibuprofen, skin decontamination, paroex, chloraprep, antimicrobial, skull base tumor, head and neck tumor, skin tumor

Initial study selection for each clinical question was performed by 2 reviewers with a multi-level screening process. Level I screening involved title and abstract review to identify potentially relevant studies for inclusion in level II screening. Level II screening was full-text review of articles to confirm relevance given the inclusion and exclusion criteria below:

Inclusion Criteria:

- Published since 1990 (01/01/1990 – 05/08/2018)
- English language
- Reported a meta-analysis/systematic review, RCT, prospective or retrospective cohort/comparative, case-control, or case series
- Reported outcomes of interest for clinical questions

- Included at least 20 patients per study and/or per arm of study
- Human subjects

Relevant clinical practice guidelines and systematic reviews underwent a separate bibliographic screen, as a cross-reference to ensure no relevant literature was excluded during the search process. These articles were screened as described above. Duplicate articles were eliminated. Studies meeting inclusion criteria were assessed for methodologic quality, as described below. Excluded studies and their reasons for exclusion were documented for review by the work group to confirm the final rejection or reconsider the study for inclusion. See Appendix Figure 1 for details.

Additional references were included in this review if considered necessary for background or discussion; however, these references were not critically appraised or used in the development of recommendation statements.

Critical Appraisal of Evidence

A modified version of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process was used to evaluate the methodologic quality of clinical studies and the strength of clinical evidence for the purposes of developing clinical practice guidelines and performance measures. GRADE determines the quality of evidence across outcomes rather than assessing each study individually. The quality of evidence for each outcome is initially determined by study design. The evidence from randomized controlled trials (RCTs) is assigned as high-quality evidence, while evidence from observational studies begin as low quality. From there, high quality evidence can be downgraded and low-quality evidence can be graded up or down based on the following: risk of bias; publication bias; imprecision related to the estimate of effect; inconsistency across studies; and indirectness related to the clinical questions. Studies on melanoma were considered but downgraded for being indirect evidence.

A total of 9,836 references were identified from databases; with 8,696 screened after excluding duplicate records. After screening and critical appraisal were performed, 20 studies were selected for final review

for this guideline. The full Quality Appraisal and Evidence Tables can be found at:

<https://plasticsurgerypsf.sharepoint.com/:b:/g/departments/quality/>

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Grading of Recommendations

Clinical practice recommendations were developed using BRIDGE-wiz (Building Recommendations in a Developers' Guideline Editor) software⁵, with consideration of the following 4 factors: 1) level of evidence (study quality); 2) assessment of benefits versus harms; and 3) patient preferences; 4) feasibility. Work group members jointly drafted statements for each recommendation during an in-person meeting in the Spring of 2018 and refined these during subsequent conference calls and online discussions. After each meeting, members had an opportunity to further individually comment and suggest revisions of the draft recommendations via email. Work group members participated in several rounds of revisions until unanimous consensus was achieved for each recommendation statement. Each recommendation in this guideline is accompanied by a grade indicating the strength of the recommendation, which was determined by considering the overall level of evidence supporting the recommendation and the judgment of the guideline developers. See Figure 1 and Table 1 in the manuscript for explanations.

Peer Review and Public Comment Process

The draft guideline was peer reviewed by the American Society of Plastic Surgeons, the American Society for Dermatologic Surgery, the American Society for Mohs Surgery, the American Academy of Otolaryngology-Head and Neck Surgery, the American Society for Clinical Oncology, and the American Society of Radiation Oncology. Peer reviewers were invited to review and provide feedback on the validity, generalizability, and clarity of the draft guideline using the Appraisal of Guidelines for Research & Evaluation Global Rating Scale (AGREE-GRS) instrument, as well as asked to support the individual recommendations. The draft guideline was also posted on the ASPS website for a 30-day public comment period, as well as distributed through the Council on Medical Specialty Societies Clinical Practice Guidelines listserv.

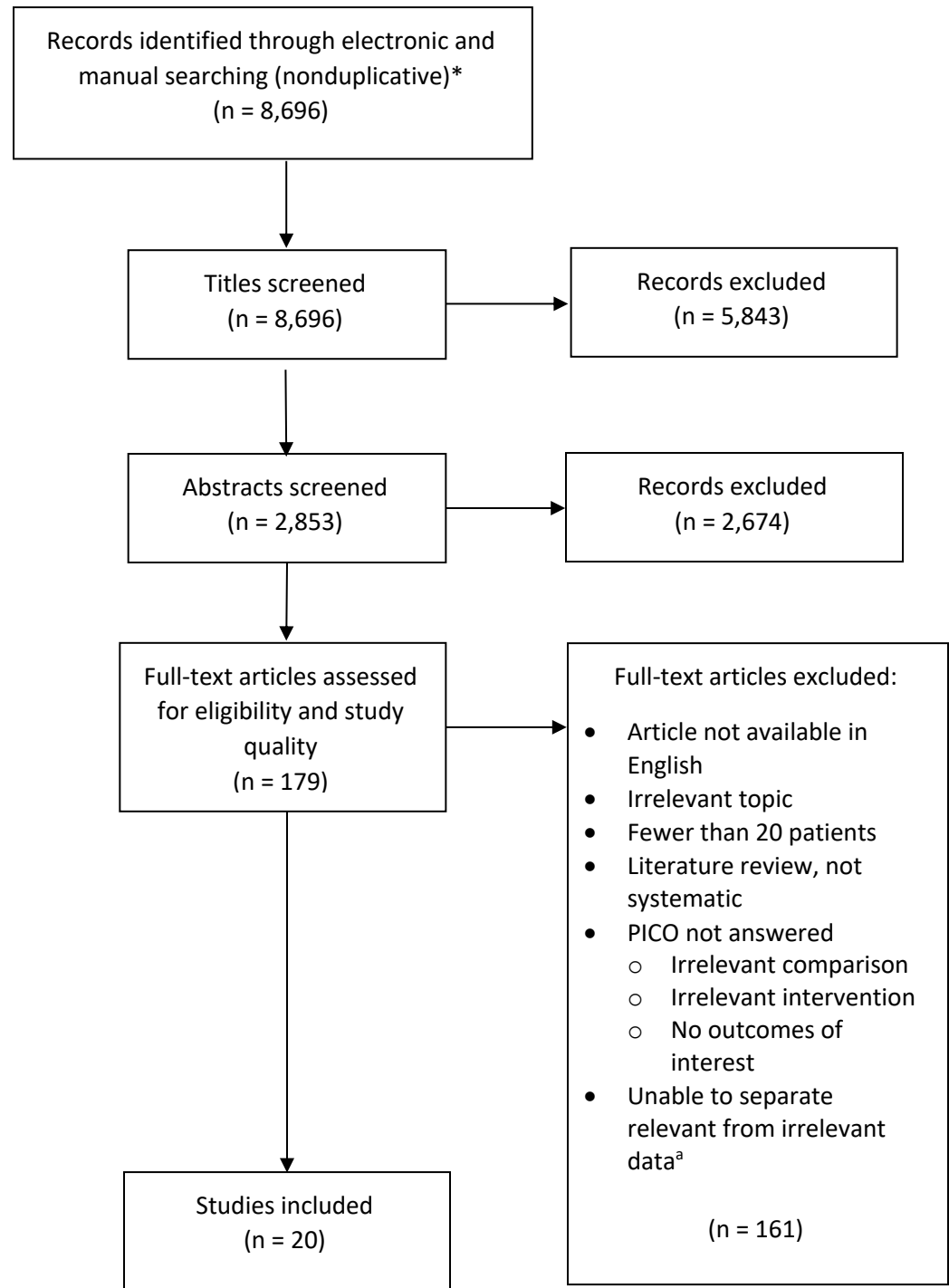
Guideline Approval Process

After the peer review and public comment process, the guideline draft was reviewed and modified by the work group after consideration of peer review and public comments. The final guideline was approved by the ASPS Executive Committee and the ASDS Board of Directors in February 2019, the AAD and ASMS Board of Directors in April 2019, and the AAO-HNS Executive Committee in May 2019. Per the project Memorandum of Understanding (MOU), the guideline was approved by all remaining parties in late April 2019.

Plan for Updating Guideline

In accordance with the inclusion criteria of the ECRI Guidelines Trust, this guideline will be updated within 5 years or in the event when newly published evidence may result in a change to current recommendations. ASPS uses a digital platform (P.E.E.R.) to store literature and data, thereby facilitating an efficient updating process.

Appendix Figure 1. Literature Search Process Charts



* Limits set in PubMed included publication date, humans, English-language, and study types; the functionalities of the other databases did not allow for limit setting.

^a Multiple studies lumped patients undergoing primary closure or second intention healing with those undergoing true reconstructive procedures; unable to cleanly extract relevant data without introducing serious issues of confounding.