Evidence-based Practice Center Systematic Review Protocol
Project Title: Strategies to Treat and Manage Infantile Hemangioma

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(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Background

Infantile hemangiomas (IHs) are the most common tumors of childhood. IHs are vascular tumors that, while benign, possess potential for local tissue destruction, infection, bleeding, and pain. Due to historical inconsistencies in naming conventions, it is difficult to understand the true prevalence of IHs, but it has been estimated that they affect about four to five percent of children,[1] with higher prevalence in females and Caucasians.[2 3] The most common locations are the head, neck, and trunk, but they can occur almost anywhere throughout the body, including deep compartments of the extremities, the spine, and visceral organs.[4-6] IHs can also be associated with a constellation of congenital anomalies such as PHACES (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft and supraumbilical raphe) PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) and LUMBAR (lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies) syndromes.

IHs tend to go through growth, plateau, and involution phases, although the complete natural history of IHs by various characteristics has not been described. IHs will become apparent in most patients in the first few weeks of life and reach 80 percent of total size by around age 3 months.[7] With a course of expectant observation, many patients may experience a complete involution without significant sequelae; however, IHs frequently occur in cosmetically and functionally sensitive areas. Even with complete involution, some patients have permanent cosmetic disfigurement and functional compromise.[8] Early assessment of the extent of the hemangioma, and early, appropriate treatment of IHs may potentially mitigate these complications. Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.[9, 10] With this rapid growth, there is little time for prospective observation to determine which hemangiomas will lead to complications and require specialist attention and treatment before complications begin to manifest. Some types of hemangiomas, specifically segmental hemangiomas such as those associated with syndromes like PHACES, are recognized as high risk, but no consensus exists on which non-segmental lesions warrant referral for appropriate treatment to mitigate future complications (e.g., bleeding, ulceration) of the hemangioma or long-term sequelae (e.g., scarring, anatomical disfigurement, functional complications).[4, 6, 11]

Evaluation through the use of various diagnostic imaging modalities has been generally been reserved for deep lesions to help understand their extent. Purely cutaneous lesions do not require imaging, but opinions regarding the initial diagnostic test of choice for more extensive IHs,

including deep, segmental, and syndromic lesions, are conflicting. Furthermore, different disease sites or extents may be best handled with different imaging modalities. The questions of imaging necessity and type are critical, as many imaging studies in infants require general anesthesia.

Specific disease characteristics, such as lesion size, location and persistence and modifiers such as patient age, functional impact, and hemangioma subtype influence whether children are treated with pharmacologic agents or surgically. Most lesions can be treated with pharmacologic agents; however, lesions that possess immediate risk for morbidity or mortality, such as hemangiomas obstructing the airway, may require more immediate surgical intervention. Potential psychosocial impact may also help determine treatment. Both medical and surgical treatment paradigms contain significant variability and lack of consensus.

In many cases of IH, early referral and intervention is crucial to a satisfactory outcome, such as ocular hemangiomas disrupting the development of neural pathways during infancy. Further, some lesions, such as nasal tip IHs, may cause permanent structural changes to adjacent structures. This may result in severe functional and cosmetic sequelae, even with complete resolution of the IH itself. In addition to structural damage, the psychological complications of having facial differences must be considered when determining the need for referral or treatment. While there are some well-recognized clinical signs that would indicate need for urgent referral, such as ulceration or airway obstruction, there are no discrete guidelines that help direct primary care providers on when to refer patients with IHs for subspecialty care.

Interventions

Propranolol was approved by the U.S. Food and Drug Administration (FDA) for use in IH in March 2014.[12-14] Prior to this, corticosteroids were the drug of choice, and there is still disagreement about which medication represents the best choice for initial medical management. Additionally, there is no clear consensus as to when alternative or adjunctive medications such as chemotherapeutic drugs are appropriate after first-line treatment is unsuccessful.[15, 16]

Surgical interventions for IH can be used for primary management of high risk lesions by resection or ablation using laser or radiofrequency. Among patients treated with surgery (including laser and resection) some confusion and disagreement exists about what type of treatment to use, when in the disease course to treat, and how the disease site informs treatment decisions. Interventions for IH are varied, involved, and not without risk (e.g., risk of permanent hypopigmentation, scarring from pulsed dye laser therapy); therefore, universal treatment is unwarranted. The decisional dilemmas that this review aims to address are whether and under what circumstances it is appropriate to treat IH, whether imaging modalities are useful in both diagnosis and for guiding treatment, and the expected comparative effectiveness of pharmacologic and surgical treatments. While pharmacologic and surgical interventions cannot be directly compared because of their inherit confounding by indication, we will assess the comparative effectiveness of different options within both pharmacologic and surgical approaches. The review will also address whether adjuvant treatment has been shown to lead to improved outcomes when initial treatment fails.

Existing Systematic Reviews and Meta-Analyses

We identified 13 treatment-focused systematic reviews or meta-analyses published in the last 10 years addressing IH (Appendix A). While several current reviews address the use of beta-blockers (e.g., propranolol) and corticosteroids, none provides a complete picture of the effectiveness and outcomes of IH treatment. Existing reviews also typically do not address questions of imaging or conservative treatment, and some focused solely on localized lesions (e.g., airway).

Objectives

This systematic review will provide a comprehensive review of both potential benefits of diagnostic modalities and surgical and pharmacologic treatments, as well as harms associated with these interventions in individuals (0-18 years) with IH or suspected IH. For this review, we have defined IH as benign vascular tumors of infancy, presenting after birth, typically characterized by early proliferation and self-involution (excluding hemangiomas fully formed at birth), which is in line with the IH classification created by Mulliken and Glowacki in 1982 and later officially adopted by the International Society for the Study of Vascular Anomalies.[17, 18] We will explore the context in which IHs present, the natural history of these lesions, and clinical factors suggesting the need for referral. We will assess the comparative effectiveness of surgical or pharmacologic interventions after initial referral and also address long-term outcomes (e.g., psychological impact on the patient, prevention of disfigurement).

II. The Key Questions

Key Questions (KQs) were developed in consultation with Key Informants and the Task Order Officer. We received one comment from the public posting of the key questions addressing the age of the population; the commenter suggested expanding the population to older children and teens to address the long-term outcomes of interventions and complications from untreated IHs for Key Questions 2-4 and the Contextual Questions (CQs). The age of the population was reworded to include patients up to 18 years of age for Key Questions 2-4 and the CQs.

Our Contextual Questions (CQs) are as follows:

CQ1. What is known about the natural history of infantile hemangiomas, by hemangioma site and subtype? What are the adverse outcomes of untreated infantile hemangiomas? What characteristics of the hemangioma (e.g., subtype, size, location, number of lesions) indicate risk of significant medical complications that would prompt immediate medical or surgical intervention?

CQ2. What is the evidence that five or more cutaneous hemangiomas are associated with an increased risk of occult hemangiomas?

Our Key Questions (KQs) are as follows:

KQ1. Among newborns, infants, and children up to 18 years of age with known or suspected infantile hemangiomas, what is the comparative effectiveness (benefits/harms) of various imaging modalities for identifying and characterizing hemangiomas?

a. Does the comparative effectiveness differ by location and subtype of the hemangioma?

KQ2. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas who have been referred for pharmacologic intervention, what is the comparative effectiveness (benefits/harms) of corticosteroids or beta-blockers?

KQ3. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas for whom treatment with corticosteroids or beta-blockers is unsuccessful what is the comparative effectiveness of second line therapies including immunomodulators and angiotensin-converting enzyme inhibitors?

KQ4. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas who have been referred for surgical intervention, what is the comparative effectiveness (benefits/harms) of various types of surgical interventions (including laser and resection)?

Table 1. PICOTS for KQ1

PICOTS	Criteria
Population	Newborns, infants, and children up to 18 years of age with known or suspected infantile hemangiomas
Intervention(s)	Diagnostic imaging: • Magnetic resonance imaging (MRI) • Computed tomography • Magnetic resonance angiography • Echocardiography • Ultrasonography • Endoscopy
Comparator	• Other workup evaluation approaches for treatment planning • Other imaging modalities
Outcomes	• Ability to identify presence, number, and extent of hemangiomas and associated structural anomalies (sensitivity and specificity) • Harms including, but not limited to, effects of sedation or imaging dye
Timing	• Immediate and short-term (≤ 3 months) • Long-term (> 3 months)
Setting	• Inpatient and outpatient settings (e.g., pediatric radiology clinic, otolaryngology clinics, dermatology clinics, pediatric surgical unit)

Abbreviations: PICOTS=Population, Intervention, Comparator, Outcomes, Timing, Setting

Table 2. PICOTS for KQs 2, 3, 4

PICOTS	Criteria
Population	Newborns, infants, and children up to 18 years of age with infantile hemangiomas
Intervention(s)	KQ2 Pharmacologic interventions • Systemic (e.g., propranolol) or topical (e.g., timolol) beta-blockers • Corticosteroids (topical, intralesional, or systemic) KQ3 Pharmacologic interventions • Immunosuppressants (e.g., sirolimus) • Immunomodulators (e.g., imiquimod, interferon) • Antineoplastics (e.g., intralesional bleomycin, intravenous vincristine) • Angiotensin-converting enzyme inhibitors • Antiangiogenic agents KQ4 Surgical interventions Laser treatment • Pulsed dye • Fractionated laser • Argon • Carbon dioxide • Neodymium (Nd): YAG • Erbium Surgical treatment • Cryotherapy • Resection • Embolization • Radiofrequency ablation therapy

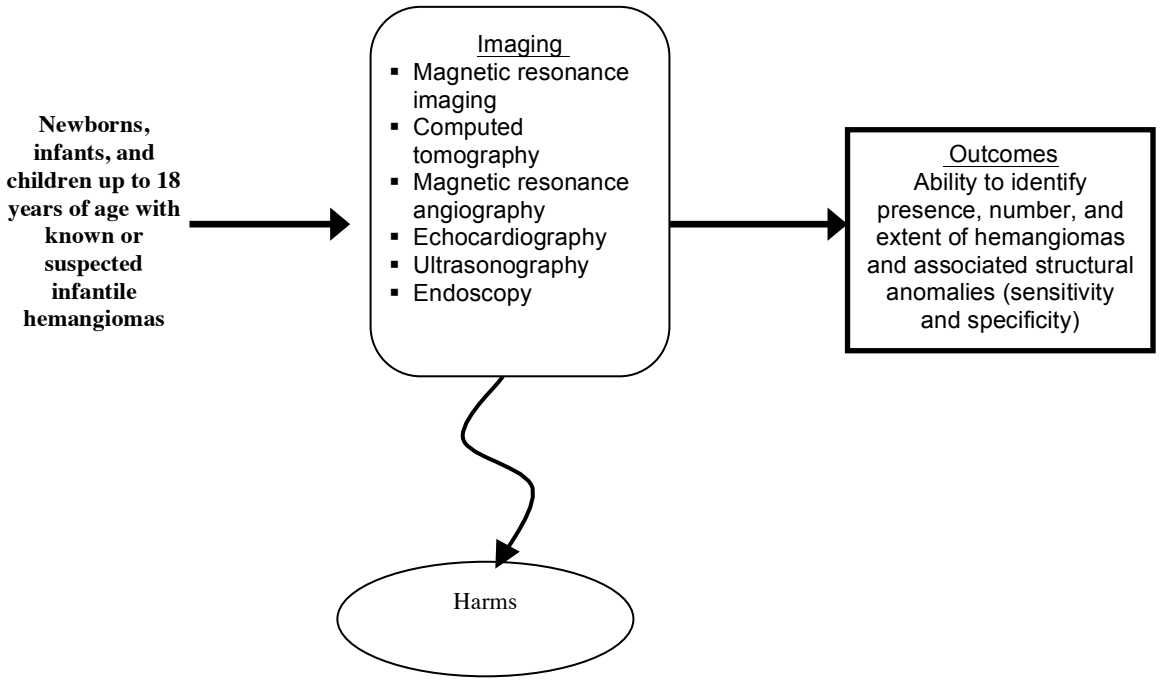
Table 2. PICOTS for KQs 2, 3, 4, continued

PICOTS	Criteria
Comparator	KQ2, 3 • No treatment • Other pharmacologic interventions • Observation • Complementary and alternative medicine (CAM) (e.g., massage, compression therapy, essential oils) KQ4 • No treatment • Other laser or surgical interventions • Observation • Complementary and alternative medicine (CAM) (e.g., massage, compression therapy, essential oils)
Outcomes	Intermediate outcomes (KQ2, 3, 4) • Size / volume of hemangioma • Impact on vision • Aesthetic appearance as assessed by clinician or parent • Degree of ulceration • Harms • Quality of life Final outcomes (KQ2, 3, 4) • Marked improvement of hemangiomas • Prevention of disfigurement • Resolution of airway obstruction • Preservation of vision • Preservation of organ function (e.g., thyroid function, cardiac function) • Resolution of ulceration • Psychological impact on the patient • Harms including: pain, bleeding, sequelae of scarring, skin atrophy, venous prominence, disfigurement, distortion of anatomic landmarks, ulceration, infection, hypopigmentation
Timing	KQ2, 3 • Immediate and short-term (≤ 2 years of age) • Long-term (> 2 years of age) KQ4 • Immediate and short-term (≤ 3 months) • Long-term (> 3 months)
Setting	• Inpatient and outpatient settings (e.g., pediatric radiology clinic, otolaryngology clinics, dermatology clinics, pediatric surgical unit)

Abbreviations: PICOTS=Population, Intervention, Comparator, Outcomes, Timing, Setting; CAM=Complementary and alternative medicine; KQ=Key Question

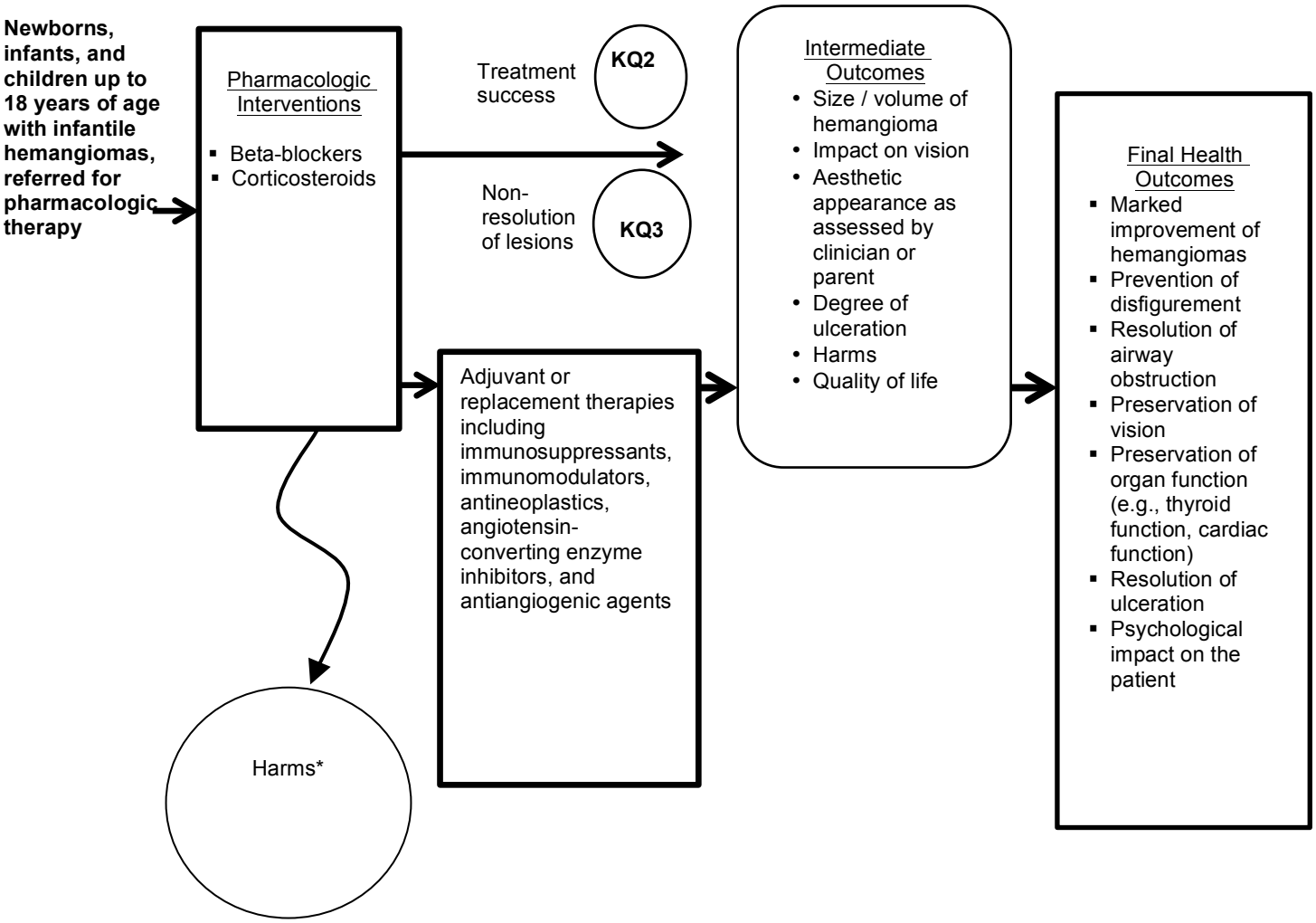
III. Analytic Framework

Figure 1. Analytic framework for KQ1, effectiveness of imaging modalities for identifying and characterizing infantile hemangiomas



Source: www.effectivehealthcare.ahrq.gov
Published online: December 23, 2014

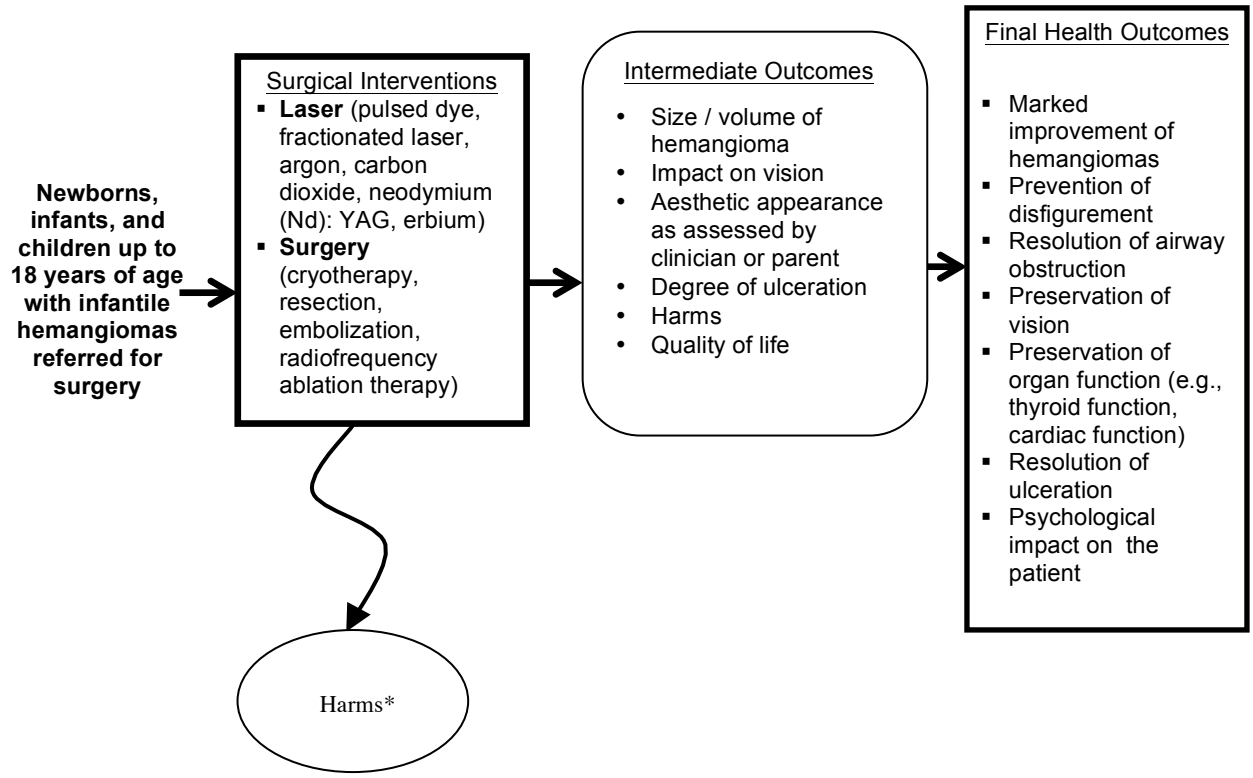
Figure 2. Analytic framework for KQ2 & KQ3, pharmacologic interventions for infantile hemangiomas



*Harms including pain, bleeding, sequelae of scarring, skin atrophy, venous prominence, disfigurement, distortion of anatomic landmarks, ulceration, infection, hypopigmentation

Note: numbers in circles on the figure indicate placement of Key Questions.

Figure 3. Analytic framework for KQ4, surgical interventions for infantile hemangiomas



*Harms including: pain, bleeding, sequelae of scarring, skin atrophy, venous prominence, disfigurement, distortion of anatomic landmarks, ulceration, infection, hypopigmentation

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We outline the inclusion/exclusion criteria selected based on our understanding of the literature, input from the topic refinement phase and content experts, and established principles of methodological quality in Table 3. Literature searches will cover publications from 1982 to present as that year marks the inception of the new classification of IHs. We will include studies published in English only. Two team members independently reviewed the titles and abstracts of the non-English language literature located via our MEDLINE search, which spanned 1982 to the present and was limited to controlled clinical trials or randomized controlled trials. We determined that the majority of the foreign language studies did not cover interventions not addressed in the English language studies. We feel that excluding non-English studies will not introduce significant bias into the review. We will, however, re-assess non-English studies as we update our MEDLINE search. The team will evaluate any additional non-English studies that appear relevant to determine how or if these studies should be addressed in the review (e.g., appendix providing relevant information gleaned from abstract).

Table 3. Inclusion Criteria

Category	Criteria
Study population	Newborns, infants, and children up to 18 years of age with infantile hemangiomas or suspected infantile hemangiomas
Publication languages	English only
Publication year	1966-present (CQ 1 & 2) 1982-present (KQ 1, 2, 3, 4)
Admissible evidence (study design and other criteria)	Admissible designs Contextual Questions: • Reviews, historical articles, practice guidelines, meta-analyses, RCTs, and comparative studies Comparative Effectiveness Questions: • Imaging accuracy: RCTs and comparative studies • Benefits of interventions: RCTs and comparative studies • Harms of interventions: RCTs, comparative studies, and case series Other criteria Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results Studies must address one or more of the following: • Diagnostic imaging (e.g., magnetic resonance imaging, computed tomography, magnetic resonance angiography, echocardiography, ultrasound, endoscopy) • Surgical interventions (e.g., cryotherapy, resection, embolization, radiofrequency ablation therapy) or laser interventions (e.g., pulsed dye, fractionated laser, argon, carbon dioxide, neodymium (Nd): YAG, erbium) • Pharmacologic interventions (e.g., beta-blockers, corticosteroids, immunomodulators, immunosuppressants, angiotensin-converting enyzme inhibitors, antiangiogenic agents, antineoplastics) • Baseline and outcome data (including harms) related to interventions for infantile hemangiomas Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (vs. individual participant data)

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Search strategies and databases

To ensure comprehensive retrieval of relevant studies addressing our comparative effectiveness questions, we will use three key biomedical databases: the MEDLINE® medical literature database via the PubMed® interface, the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and EMBASE (Excerpta Medica Database), an international biomedical and pharmacologic literature database via the Ovid® interface. As precise controlled vocabulary terms for IH are not defined in the Medical Subject Headings (MeSH) used in PubMed, Cumulative Index to Nursing and Allied Health (CINAHL) medical subject headings, or the Emtree thesaurus used in EMBASE, search strategies will use a combination of keywords and controlled vocabulary terms. Moreover given the importance of capturing studies addressing long-term outcomes in older children and youth, the searches are constructed to capture publications on patients beyond infancy when IHs arise.

To address the contextual questions separately from the comparative effectiveness questions, the team has defined two separate search strategies. Searches will be conducted in the same bibliographic databases. For the contextual questions, searches will broadly seek studies within systematic and narrative reviews, practice guidelines, and meta-analyses (Appendix B, Tables 1-3). Applicable comparative studies retrieved through the comparative effectiveness search will be flagged for the contextual questions. No year limits will be applied to the contextual question searches; PubMed, EMBASE, and CINAHL will be searched from the database inception (1966, 1974 and 1981 respectively) to the present.

Searches for comparative effectiveness include terms to address harms (Appendix B, Tables 4-6). Based on input from Key Informants (KIs) specific therapeutic intervention terms have been added to the search strategies. KIs also suggested starting comparative effectiveness searches at 1982, which is the start date for modern classification of IHs.

All searches will be created by an expert librarian and reviewed by a second expert librarian. Preliminary searches in PubMed/MEDLINE, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and EMBASE (Excerpta Medica Database) are presented in Appendix B, Tables 1-6.

Search updates. We will update the searches when the draft report is submitted and will add relevant studies as needed while the draft report is undergoing peer review. We will also incorporate studies that meet our inclusion criteria or are relevant as background material that may be identified by both public and peer reviewers.

Hand searching. We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of diagnostic modalities and therapies for IHs. The investigative team will also scan the reference lists of articles that are included after the full-text review phase for studies that potentially could meet our inclusion criteria.

Grey literature. We will conduct searches of the grey literature including, but not limited to, Web Sites of agencies/organizations conducting research or involved in policy or guidance in the area. These will include professional organizations such as the American Academy of Dermatology (AAD), the American Society of Pediatric Otolaryngology (ASPO), the International Society for the Study of Vascular Anomalies (ISSVA), the National Organization of Vascular Anomalies (NOVA), and the Vascular Birthmarks Foundation (VBF). We will also

search other sources (e.g., Clinicaltrials.gov, the Food and Drug Administration) for context and relevant data, as well as ongoing trials. We will review citations provided via these searches against our criteria for potential inclusion.

Scientific Information Packets. We will request Scientific Information Packets (SIP) (Appendix C) and regulatory information addressing medications with FDA-approval for IHs, including propranolol (Hemangeol™), timolol, gel-forming timolol (Timolol GFS, Timoptic-XE®), dexamethasone sodium phosphate, prednisone, prednisolone (Flo-Pred), sirolimus (Rapamune®), imiquimod (Aldara®), interferon alpha (Intron A®), captopril, bleomycin (Blenoxane®), vinblastine, vincristine (Vincasar PFS), Avastin®, Regranex® (Becaplermin), and Sotradecol, and devices for laser treatment of IHs including pulsed dye lasers, Vbeam®, argon, carbon dioxide lasers(CO_2), Nd: YAG (Neodymium Yttrium Aluminum Garnet ND YAG), and erbium YAG laser. We will review citations provided via these searches against our criteria for potential inclusion.

C. Data Abstraction and Data Management

Screening and extraction forms

We will develop forms for screening (abstract and full-text review) and data extraction. The forms used for the abstract review will contain questions about the primary exclusion and inclusion criteria. The forms used for the full-text review are more detailed and are intended to identify studies that meet inclusion criteria and assist in initially sorting the studies according to the KQs.

We will create data extraction forms to collect detailed information on the study characteristics, intervention(s), comparator(s), arm details, reported outcomes and outcome measures, and study quality. The forms will include all the information necessary to generate summary tables, create evidence tables, and perform data synthesis.

Initial review of abstracts

We will review all the titles and abstracts identified through our searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information to make the determination, we will retrieve the full-text articles and review them against the inclusion/exclusion criteria.

Retrieving and reviewing articles

We will retrieve and review all articles that meet our predetermined inclusion criteria or for which we have insufficient information to make a decision about eligibility. Each article will be reviewed by at least two members of the investigative team. Differences between the reviewers will be adjudicated by a senior team member.

We will develop a simple categorization scheme for coding the reasons that articles at full review are excluded. We will then record those codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database so that we can later compile a listing of excluded articles and the reasons for such exclusions.

Data extraction

For studies that meet the conditions of the full-text review assessment, the extractors will extract study characteristics (e.g., study design, year, intervention characteristics) from the articles. We will deposit the data used in the meta-analyses into the Systematic Review Data

Repository (SRDR). As noted above, we anticipate that these elements will include population and intervention characteristics such as age, intervention approach, and outcomes. A second reviewer will review the initial data extraction against the original articles for quality control. Differences in data coding between the extractor and the reviewer will be resolved by consensus.

Few studies of IH use validated or objective tools to measure outcomes. Studies frequently report investigator or parent-rated improvements in color and texture or degree of ulceration assessed using serial photographs. Changes in size or volume are generally reported in centimeters or millimeters or centimeters/millimeters squared with measurement using flexible rulers. We will focus on reporting objective measurements but will include observer-rated measurements given the importance of aesthetic improvement to parents and children, and clinician reliance on these measures as indictors of treatment trajectory.

We will extract at minimum the characteristics and primary outcomes (where reported on objective or observer-rated scales) outlined in Tables 4 and 5 for included studies. A second reviewer will review the extracted data for quality control. Conflicts between data abstractors will be resolved by consensus.

Table 4. Population/intervention characteristics and outcomes of interest KQ1

KQ	Characteristics	Primary Outcomes
1	• Newborns, infants, and children up to 18 years of age with known or suspected infantile hemangiomas • Immediate and short-term (≤ 3 months) or Long-term (> 3 months) • Inpatient and outpatient settings (e.g., pediatric radiology clinic, otolaryngology clinics, dermatology clinics, pediatric surgical unit)	• Ability to identify presence, number, and extent of hemangiomas and associated structural anomalies (sensitivity and specificity) • Harms

Table 5. Population/intervention characteristics and outcomes of interest KQ2-4

KQ	Characteristics	Primary Outcomes	Secondary Outcomes
2-3	• Newborns, infants, and children up to 18 years of age with infantile hemangiomas • Immediate and short-term (≤ 2 years of age) • Long-term (> 2 years of age) • Inpatient and outpatient settings (e.g., pediatric radiology clinic, otolaryngology clinics, dermatology clinics, pediatric surgical unit)	• Size / volume of hemangioma • Impact on vision • Aesthetic appearance as assessed by clinician or parent • Degree of ulceration • Harms	• Quality of life
4	• Newborns, infants, and children up to 18 years of age with infantile hemangiomas • Immediate and short-term (≤ 3 months) or Long-term (> 3 months) • Inpatient and outpatient settings (e.g., pediatric radiology clinic, otolaryngology clinics, dermatology clinics, pediatric surgical unit)	• Size / volume of hemangioma • Impact on vision • Aesthetic appearance as assessed by clinician or parent • Degree of ulceration • Harms	• Quality of life

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the risk of bias of studies addressing comparative effectiveness questions. We will assess key outcomes of interest specified in the PICOTS above using criteria from established tools and the Methods Guide for Effectiveness and Comparative Effectiveness

Reviews.[19] Two senior investigators will independently assess each included study. Disagreements between assessors will be resolved through discussion.

We will use the risk of bias tools defined in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions[20] derived from the RTI Item Bank to assess risk of bias for randomized controlled trials of effectiveness, controlled clinical trials/cohorts, and case-control studies. For comparative and non-comparative studies, the tool includes 9 to 13 items from six domains of potential sources of bias (i.e., selection, performance, attrition, detection and reporting). We will use the McMaster Quality Assessment Scale of Harms (McHarm) tool to assess harms studies.[21] To assess the risk of bias associated with the reporting of diagnostic accuracy, we will use the 14-item QUADAS tool.[22] We will describe study quality as "good," "fair," or "poor" using pre-established thresholds for risk of bias assessments.[23]Two senior investigators will independently assess each included study. Disagreements between assessors will be resolved through discussion. We will report findings of poor quality studies in evidence tables but will focus our analyses on those studies with lower risk of bias, i.e., studies of good or fair quality as determined in our quality assessment process.

We will not rate the quality of studies that address the contextual questions.

E. Data Synthesis

Synthesizing results

We will provide a qualitative synthesis of studies meeting our review criteria. Our preliminary assessment of the literature suggests that we may also be able to use meta-analytic techniques after transforming outcomes into standardized measures in order to assess effectiveness. This approach will have the benefit of allowing us to combine studies that use different specific measures for the same outcomes; it suffers to some degree in clinical interpretability but our clinical experts will assist in placing meta-analytic results in context for our end users. The specific meta-analysis or meta-regression will depend on the data available.

We will refine our analytic approach as we gather more data on the available literature. It is likely that analyses will be combined using a hierarchical mixed effects model. Hierarchical random effects allow results from individual studies to be partially pooled, meaning that each study can contribute to inference in the meta-analysis without tenuously assuming that the set of studies are identical. These random effects will allow both an estimate of the overall (population) effect as well as an estimate of the variance of the effect across studies, after controlling for available study-level covariates.

Quantifying study-level heterogeneity via random effects is preferable to the use of an arbitrary variance cutoff value or statistical tests for heterogeneity, such as Q statistics or I^2 scores. The decision of whether to partially pool a set of studies using random effects depends not on how heterogeneous their outcomes are, but rather, whether they can be considered exchangeable studies from a population of studies of the same phenomenon. This should be determined based on the design and quality of the studies, independently of the studies' relative effect sizes.

Some differences among study populations may be accounted for in the model by adjusting for factors such as age distribution, demographic attributes, and the prevalence of concomitant conditions in the study sample. Newer approaches to random effects meta-analysis, such as latent Dirichlet process and Gaussian process models, allow for robust (e.g., non-parametric) estimates

of variation that do not rely on the assumption of normally-distributed random effects. This permits us to account for "outlier" studies in the meta-analytic model without either discarding them unnecessarily or allowing them to disproportionately influence meta-estimates. Additionally, publication bias can bias the distribution of outcomes away from a normal distribution.

We anticipate that due to fundamental differences among classes of treatment (e.g., pharmacologic, surgical, laser) and diagnostic interventions (e.g., magnetic resonance imaging, computed tomography, magnetic resonance angiography, echocardiography, ultrasound) we will use separate meta-analytic models for each. Within intervention classes, however, it may be possible to pool subsets of studies, conditional on a suite of covariates that, when properly modeled, can be considered exchangeable (conditionally independent given a set of study-level covariates). Care must be taken in assigning the membership of each study to one of a reasonably small set of intervention classes. It will be important to test the sensitivity of our meta-analytic models to misclassification error, or to pooling studies into classes that are too heterogeneous (i.e., too few classes in the set).

Analysis of subgroups will be done formally, within a statistical model, or by stratifying results and organizing the report in such a way that end users are provided with both overall outcomes data and information specific to subgroups defined by factors such as hemangioma location that can be easily identified and stand alone as needed. Subgroup analysis may be used to evaluate the intervention effect in a defined subset of the participants in a trial, or in complementary subsets. Subgroup analysis can be undertaken in a variety of ways, from completely separate models at one extreme, to simply including a subgroup covariate in a single model at the other, with multilevel and random effects models somewhere in the middle.[24, 25] Generally, trial sizes are too small for sub-group analyses within individual studies to have adequate statistical power.

Meta-regression models describe associations between the summary effects and study-level data; that is, it describes only between-study and not between-patient variation. We would use multilevel models, which boost the power of the analysis by sharing strengths across subgroups for variables where it makes sense to do so, or subgroup analysis (with random effects meta-analysis) to explore heterogeneity if there are a sufficient number of studies. When the sizes of the included studies are moderate or large, each subgroup should have at least 6 to 10 studies for a continuous study-level variable and a minimum of four studies for a categorical study-level variable. These numbers serve as a rule of thumb for the lower bound for number of studies that investigators would consider for a meta-regression, but power will vary according to the size and variability of the effect.

Presentation of results

Within each KQ, we will organize results by study design and outcome, with a focus on those designs less subject to bias (i.e., randomized controlled trials, controlled trials), those studies rated as having higher quality in our quality assessment process, and those employing comparison groups.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will use explicit criteria for rating the overall strength of the evidence for each primary intervention-outcome pair for which the overall risk of bias is not overwhelmingly high. We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-

sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will not rate the SOE for studies addressing contextual questions.

The strength of evidence evaluation will be that stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews,*[19] and in the updated strength of evidence guide[23]which emphasizes the following five major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct, indirect), and precision (precise, imprecise), and reporting bias (present, undetected). When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient.

Risk of bias is derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome for each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains. We will assess reporting bias of RCTs by examining outcomes of trials as reported in resources such as ClinicalTrials.gov to determine if pre-specified outcomes are not reported in the published literature.

The overall strength of evidence will be graded as:

Strength of evidence grades and definitions[23]

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing results for each outcome.

G. Assessing Applicability

We will assess the applicability of findings reported in the included literature to the general population of children up to age 18 years with IH by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipate that areas in which applicability will be especially important to describe will include the severity and anatomic location of IH in the study population and the age range of the participants. We will also attempt to capture information about the clinical provider including specialty and training. We anticipate variation in reporting of IH and variation in reporting of outcomes. The classification surrounding vascular malformations and vascular tumors, such as IH, have been inconsistent in the past. By limiting our literature search to articles published in or after 1982, when naming was more standardized, we hope to minimize this.

Additionally, the indications for treatment of IHs in the past and in the era of propranolol may have changed, introducing a bias for treatment sooner and for less severe IH conditions.

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VI. Definition of Terms

AAD: American Academy of Dermatology
AHRQ: Agency for Healthcare Research and Quality
ASPO: American Society of Pediatric Otolaryngology
CAM: Complementary and alternative medicine
CINAHL: Cumulative Index to Nursing and Allied Health
CQ: Contextual question
EPC: Evidence-based Practice Center
FDA: U.S. Food and Drug Administration
IH: Infantile hemangioma
IHs: Infantile hemangiomas
ISSVA: International Society for the Study of Vascular Anomalies
KI: Key Informant
KQ: Key Question
LUMBAR: lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, renal anomalies syndromes
MeSH: Medical Subject Headings
NMA: Network meta-analysis
NOVA: National Organization of Vascular Anomalies
PELVIS: the perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag
PHACES: Posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe
PICOTS: Population, Intervention, Comparator, Outcomes, Timing, Setting
SIP: Scientific Information Packets
SOE: Strength of Evidence
SRC: Scientific Resource Center
SRDR: Systematic Review Data Repository
TOO: Task Order Officer
VBF: Vascular Birthmarks Foundation

VII. Summary of Protocol Amendments

Date	Amendment	Rationale
12-5-2014	We will change our inclusion criteria to include case series with at least 25 children with IH. We will exclude those case series with <25 children with IH.	Because of the numerous possible harm outcomes, we cannot determine a specific sample size that would be suitable for finding statistically significant evidence of harm (or absence of harm); thus, we set a conservative limit that balances the need for smaller studies of specialized populations with the need for studies with sample sizes large enough to measure effects of the intervention.
12-17-2014	We will include the Newcastle-Ottawa Scale as a tool to assess cohort or case-control studies.	A number of studies identified in our initial screening are retrospective observational studies, and the Newcastle-Ottawa Scale may offer questions better suited for assessing these studies. We will include the questions/tools used to assess the risk of bias of all studies as an appendix to the report.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA 290-2012-1200009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Overview of reviews

Table A-1. Overview of reviews

Review	Intervention/Focus	Study designs included	Studies included
Lou et al. (2014)[1]	Propranolol vs. steroids; propranolol vs. vincristine; propranolol vs. laser for IH in all sites in body	No restrictions	35
Wat et al. (2014)[2]	Intense pulsed light therapy for dermatologic disease, including IH	No restrictions	13 studies addressing capillary and vascular lesions—6 case reports
Fette (2013)[3]	Propranolol as first line, adjuvant or second line therapy	No restrictions	27 -- 23 case series
Gunturi et al. (2013)[4]	Propranolol for IH	No restrictions	Case studies, case series and controlled trials
Izadpanah et al. (2013)[5]	Propranolol vs. corticosteroids for IH	No restrictions	56 -- 16 meta-analyses
Marqueling et al. (2013)[6]	Propranolol for IH	Any study with ≥10 cases IH	41—mostly case series
Menezes et al. (2011)[7]	Propranolol for IH	No restrictions	28—mostly case series
Xu et al. (2013)[8]	Beta-blockers vs. corticosteroids for IH	Comparative designs	10
Vlastarakos et al. (2012)[9]	Propranolol for airway IH	No restrictions	17—7 case reports
Leonardi-Bee et al. (2011)[10]	Any intervention for IH	RCTs	4
Peridis et al. (2011)[11]	Propranolol for airway IH	No restrictions	13—10 case reports
Prasetyono et al. (2011)[12]	Intralesional steroids as stand-alone therapy or adjuvant to surgery for head and neck hemangiomas	No restrictions	22
Spiteri Cornish et al. (2011)[13]	Propranolol for periocular IH	No restrictions	19—no RCTs

References for Table A-1. Overview of reviews

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Appendix B. Preliminary Search Strategies

Searches for Contextual Questions

Table 1. PubMed search strategies (PubMed web interface) (October 16, 2014)

	Search Terms	Results
#1	hemangioma, capillary infantile[nm] OR infantile hemangioma*[tiab] OR infantile haemangioma*[tiab] OR capillary hemangioma*[tiab] OR capillary haemangioma*[tiab]	2,203
#2	infant[mh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR child[mh] OR Children[tiab] OR youth[tiab] OR pediatric[tiab] OR neonat*[tiab]	2,350,052
#3	#1 AND #2	1,435
#4	#3 AND eng[la]	1,259
#5	#4 AND Humans[mh]	1,079
#6	#5 AND (review[pt] OR historical article[pt] OR practice guideline[pt] OR meta-analysis[pt])	178

Key: [mh] medical subject heading; [nm] supplementary concept; [tiab] keyword in title or abstract; [la] language; [pt] publication type; [sh] subheading

Table 2. CINAHL search strategies (EBSCO Host interface) (October 16, 2014)

	Search Terms	Results
#1	(MH "Hemangioma") OR "infantile hemangioma" OR "infantile hemangiomas" OR "infantile haemangiomas" OR "infantile haemangiomas"	975
#2	(MH " Infant, Newborn, Diseases") OR (MH "Infant") OR (MH "Infant, Newborn") OR (MH "Child") OR "infant" OR "infants" OR "infantile" OR "newborn" OR "child" OR "children" OR "pediatric" or "neonat*"	379,478
#3	S1 AND S2	424
#4	S3 AND limiters: English language	421
#5	S4 AND limiters: Exclude MEDLINE records	81

Key: MH CINAHL medical subject heading

Table 3. EMBASE search strategies (OvidSP interface) (October 16, 2014)

	Search Terms	Results
#1	Capillary hemangioma / or infantile hemangioma.tw. or infantile hemangiomas.tw. or infantile haemangioma.tw. or infantile haemangiomas.tw. or haemangioma.tw. or hemangiomas.tw.	10,830
#2	Infant/ or child/ or newborn/ or congenital disorder/ or infant*.tw. or infantile.tw. or child.tw. or children.tw. or newborn.tw. or newborns.tw.	2,275,444
#3	1 AND 2	4,191
#4	Limit 3 to English	3,353
#5	Limit 4 to human	3,094
#6	5 not (editorial.pt. or letter.pt. or note.pt. or short survey.pt. or conference paper.pt.)	927
#7	Limit 6 to exclude MEDLINE journals	97

Key: / Emtree heading; .tw. abstract, title and drug trade name; pt. publication type

Searches for Comparative Effectiveness Questions

Table 4. PubMed search strategies (PubMed web interface) (August 19, 2014)

	Search Terms	Results
#1	hemangioma[mh] OR hemangioma, capillary infantile[nm] OR infantile hemangioma*[tiab] OR infantile haemangioma*[tiab] OR capillary hemangioma*[tiab] OR capillary haemangioma*[tiab] OR congenital hemangioma*[tiab] OR congenital haemangioma*[tiab] OR IH[tiab]	33,062
#2	Infant[mh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR pediatric[tiab] OR neonat*[tiab] OR child[mh] OR children[tiab] OR youth[tiab]	2,335,431
#3	Therapeutics[mh] OR therapy[sh] OR Treatment Outcome[mh] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR therapeutics[tiab] OR outcome[tiab] OR outcomes[tiab] OR surgical[tiab] OR surgery[sh] OR surgery[tiab] OR Embolization, Therapeutic[mh] OR embolization[tiab] OR embolization[tiab] OR cryotherapy[mh] OR cryotherapy[tiab] OR Catheter Ablation[mh] OR radiofrequency ablation[tiab]OR Laser, dye [mh] OR Laser, Gas/therapeutic use[mh] OR Laser Therapy[mh] OR “carbon dioxide laser”[tiab] OR “carbon dioxide lasers”[tiab] OR CO2 laser[tiab] OR CO2 lasers[tiab] OR “fractionated laser”[tiab] OR “fractionated lasers”[tiab] OR argon[tiab] OR Lasers, Solid-State[mh] OR Neodymium YAG[tiab] OR YAG[tiab] OR Erbium[tiab] OR propranolol[mh] OR propranolol[tiab] OR timolol[mh] OR timolol[tiab] OR Imiquimod[NM] OR Adrenergic beta-Antagonists[mh] OR Angiotensin-converting enzyme inhibitors[mh] OR Immunosuppressive agents[mh] OR Angiogenesis Inhibitors[mh] OR Bleomycin[mh] OR bleomycin[tiab] OR Antineoplastic agents[mh] OR Vincristine[mh] OR vincristine[tiab] OR corticosteroids[tiab] OR beta-blockers[tiab] OR beta blockers[tiab] OR beta blocker[tiab] OR beta-blockers[tiab] OR angiotensin[tiab] OR intralesional interferon[tiab] OR “adverse effects"[Subheading] OR unsafe[tiab] OR safety[tiab] OR harm[tiab] OR harms[tiab] OR harmful[tiab] OR complication[tiab] OR complications[tiab] OR side-effect[tiab] OR "side-effects"[tiab] OR Undesirable effect[tiab] OR undesirable effects[tiab] OR undesirable reaction[tiab] OR undesirable reactions[tiab] OR undesirable event[tiab] OR undesirable events[tiab] OR undesirable outcome[tiab] OR undesirable outcomes[tiab] OR adverse effect[tiab] OR adverse effects[tiab] OR adverse reaction[tiab] OR adverse reactions[tiab] OR adverse event[tiab] OR adverse events[tiab] OR adverse outcome[tiab] OR adverse outcomes[tiab] OR "Postoperative Complications"[Mesh] OR postoperative complication[tiab] OR postoperative complications[tiab] OR post operative complication[tiab] OR post operative complications[tiab] OR surgical complication[tiab] OR surgical complications[tiab] OR postsurgical complication[tiab] OR postsurgical complications[tiab] OR post surgical complication[tiab] OR post surgical complications[tiab] OR adverse effects[Subheading] OR complications[Subheading] OR contraindications[Subheading] OR bleeding[tiab] OR Hemorrhage[mh] OR scarring[tiab] OR scars[tiab] OR residual hemangiomas[tiab] OR residual hemangioma[tiab] OR residual haemangioma[tiab] OR residual haemangiomas[tiab] OR pain[mh] OR pain[tiab] OR “Skin atrophy”[tiab] OR venous prominence[tiab] OR facial injuries[mh] OR skin ulcer[mh] OR ulceration[tiab] OR “surgical wound infection”[mh] OR wound infection[mh] OR infection[tiab]	10,334,120
#4	#1 AND #2 AND #3	7392
#5	#4 AND eng[la]	5441
#6	#5 AND Humans[mh]	5203
#7	#6 AND ("1982/01/01"[Date - Publication] : "3000"[Date - Publication])	4358
#8	#7 NOT (editorial[pt] OR letter[pt] OR comment[pt] OR review[pt] OR news[pt] OR historical article[pt] OR practice guideline[pt] OR meta-analysis[pt])	3409

Key: [mh] medical subject heading; [nm] supplementary concept; [tiab] keyword in title or abstract; [la] language; [pt] publication type; [sh] subheading

Table 5. CINAHL search strategies (EBSCO Host interface) (August 19, 2014)

	Search Terms	Results
#1	(MH "Hemangioma") OR (MH "Hemangioma, Cavernous") OR "infantile hemangioma" OR "infantile hemangiomas" OR "infantile haemangiomas" OR "infantile haemangiomas" OR "IH"	1,163
#2	(MH " Infant, Newborn, Diseases") OR (MH "Infant") OR (MH "Infant, Newborn") OR "infant" OR "infants" OR "infantile" OR "newborn" OR "pediatric" OR "neonat*" OR (MH "Child") OR "child" OR "children"	376,639
#3	S1 AND S2	452
#4	S3 AND limiters: English language	449
#5	S4 AND limiters: 1982-	448
#6	S5 AND limiters: Exclude MEDLINE records	90

Key: MH CINAHL medical subject heading

Table 6. EMBASE search strategies (OvidSP interface) (August 19, 2014)

	Search Terms	Results
#1	Capillary hemangioma / or infantile hemangioma.tw. or infantile hemangiomas.tw. or infantile haemangioma.tw. or infantile haemangiomas.tw. or haemangioma.tw. or hemangiomas.tw. or IH.tw.	15,410
#2	Infant/ or child/ or newborn/ or congenital disorder/ or infant*.tw. or infantile.tw. or child.tw. or children.tw. or newborn.tw. or newborns.tw. or neonat*.tw	2,316,140
#3	1 AND 2	4,615
#4	Limit 3 to English	3,756
#5	Limit 4 to human	3,343
#6	5 not (review.pt. or editorial.pt. or letter.pt. or note.pt. or short survey.pt. or conference paper.pt. or meta analysis/ or practice guideline/ or systematic review/)	2,699
#7	Limit 6 to 1982-	2645
#8	Limit 7 to exclude MEDLINE journals	207

Key: / Emtree heading; .tw. abstract, title and drug trade name; pt. publication type

Appendix C. Scientific Information Packets

Table C-1 Scientific Information Packets

Pharmacologic Agents – Beta Blockers	Company or Researcher Names	Contact Information
Propranolol	TOCRIS – a biotechne brand	Tocris Bioscience Tocris House, IO Centre Moorend Farm Avenue Bristol, BS11 0QL United Kingdom General Enquiries: info@tocris.co.uk Tel: + 44 (0)117 916-3333
Hemangeol™	Pierre Fabre	Pierre Fabre Pharmaceuticals 8 Campus Drive Parsippany, NJ 07054 Tel: (973) 898-1042
Hemangeol	Roxane Laboratories, Inc.	Boehringer Ingelheim Roxane, Inc. 1809 Wilson Road PO 16532 Columbus, OH 43228 Tel: (614) 276-4000
Timolol	Bausch & Lomb Incorporated	Bausch & Lomb 1400 N. Goodman St. Rochester, NY 14609 Consumer Affairs 1-800-553-5340 Fax: 585-338-6896
Timolol GFS	Falcon Pharmaceuticals, Ltd.	Falcon Pharmaceuticals, Ltd. 6201 South Fwy Fort Worth, TX 76134 Tel: (855) 424-8886
Timoptic-XE	Valeant Pharmaceuticals, International, Inc.	Valeant Pharmaceuticals, International, Inc. 400 Somerset Corporate Blvd. Bridgewater, NJ 08807 Tel: (908) 927-1400
Pharmacologic Agents - Corticosteroids	**Company or Researcher Names**	**Contact Information**
Dexamethasone Sodium Phosphate	FRESENIUS KABI	Fresenius Kabi USA Three Corporate Drive Lake Zurich, IL 60047 Main Phone (847) 550-2300 Tel: (888) 391-6300
Prednisone Intensol	Roxane Laboratories, Inc.	Boehringer Ingelheim Roxane, Inc. 1809 Wilson Road PO 16532 Columbus, OH 43228 Tel: (614) 276-4000
Flo-Pred (Prednisolone)	TARO	Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive Hawthorne, NY 10532 Tel: (800) 544-1449

Pharmacologic Agents – Immunosuppressants	Company or Researcher Names	Contact Information
Rapamune (Sirolimus)	Pfizer	Customer Service and Product Inquiries: 1-800-TRY-FIRST (1-800-879-3477) Monday through Friday 8:00 a.m. to 8:00 p.m. EST Corporate Office: Tel: (212) 733-2323 235 East 42nd Street New York, NY 10017
Pharmacologic Agents – Immunomodulators	**Company or Researcher Names**	**Contact Information**
ALDARA (Imiquimod)	Medicis	Manufactured by 3M Health Care Limited Loughborough LE11 1EP England Manufactured for Medicis, The Dermatology Company Scottsdale, AZ 85256 Tel: (800) 321-4576 Fax: (908) 927-1926 Medical Information (877) 361-2719
Intron A® (Interferon Alpha-2b)	Merck & Co, Inc	Merck Corporate Headquarters One Merck Drive PO Box 100 Whitehouse Station, NJ 08889-0100 Tel: (908) 423-1000
Pharmacologic Agents – Angiotensin-converting Enzyme Inhibitors	**Company or Researcher Names**	**Contact Information**
Captopril	APOTEX-CORP	Apotex Inc. Toronto, Ontario Canada M9L 1T9 Manufactured for Apotex Corp. Weston, FL 33326 Tel: (800) 706-5575
Pharmacologic Agents – Antineoplastics	**Company or Researcher Names**	**Contact Information**
Blenoxane® (Bleomycin)	Bristol-Myers Squibb	Bristol-Myers Squibb 345 Park Avenue New York, NY 10154 Tel: (212) 546-4000
Vinblastine	Fresenius Kabi, USA	Fresenius Kabi USA Three Corporate Drive Lake Zurich, IL 60047 Main Phone (847) 550-2300 Tel: (888) 391-6300
Vincasar PFS (Vincristine)	TEVA Pharmaceuticals	Teva North America 1090 Horsham Road North Wales, PA 19454 Tel: (888) 888-2872

Pharmacologic Agents – Antiangiogenic	Company or Researcher Names	Contact Information
Avastin®	Genentech	Genentech, Inc. 1 DNA Way, M/S 245C South San Francisco, CA 94080 Tel: (650) 225-1000 Fax: (650) 225-6000
Pharmacologic Agents – Platelet derived growth factor	**Company or Researcher Names**	**Contact Information**
Regranex® (Becaplermin)	Smith & Nephew	Smith & Nephew, Inc. 150 Minuteman Road Andover, MA 01810 Tel: (978) 749-1000 Fax: (978) 749-1599
Pharmacologic Agents – Other	**Company or Researcher Names**	**Contact Information**
Sotradecol® (Sodium Tetradecyl Sulfate)	Bioniche Pharma Group	Bioniche Pharma USA, LLC 272 Deerpath Rd. #304 Lake Forest, IL 60045 Tel: (847) 739-3246
Devices- Lasers	**Company or Researcher Names**	**Contact Information**
Dermatological Pulsed dye laser	DEKA Medical Lasers	DEKA m.e.l.a. srl via baldanzese, 17 50041 - calenzano (fi) Tel: +39 055 8874942 Fax: +39 055 8832884 info@dekalaser.com
Vbeam® (Pulsed dye laser)	Syneron and Candela	Syneron and Candela 530 Boston Post Road Wayland, MA 01778 Tel: (508) 358-7400 Tel: (800) 733-8550 Fax: (508) 358-5602
Argon	National Laser Co.	175 West 2950 South Salt Lake City, UT 84115 United States Tel: (801) 467-3391 Fax: (801) 467-3394
Carbon dioxide lasers (CO_2)	SYNRAD	Synrad, Inc. 4600 Campus Place Mukilteo, WA 98275 USA Tel: 1.425.349.3500 Fax: 1.425.349.3667 Toll Free: 1.800.SYNRAD1 E: synrad@synrad.com
Nd:YAG laser (Neodymium Yttrium Aluminum Garnet Nd YAG)	Fotona	Fotona d.d. Stegne 7 1000 Ljubljana SLOVENIA, EU Tel: + 386 1 500 91 00 Fax: + 386 1 500 92 00
Erbium YAG Laser	Fotona	Fotona d.d. Stegne 7 1000 Ljubljana SLOVENIA, EU Tel: + 386 1 500 91 00 Fax: + 386 1 500 92 00