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Development and Evidence-Based Validation of a Comprehensive Framework for Neurointerventional Laboratory Certification: The 6P Protocol Systematic Review

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Abstract

Background and Objectives—Neurointerventional laboratory standards vary significantly worldwide, lacking comprehensive evidence-based certification frameworks. We developed and validated a novel 6P Protocol (People, Place, Products, Protocols, Performance, Protection) encompassing 33 evidence-based standards for neurointerventional laboratory certification.
Methods—We developed the 6P Protocol through a modified Delphi process involving 15 international experts. The framework underwent external validation by 7 independent experts. We conducted systematic evidence review of 33 subsections using 142 high-quality studies. Evidence quality was classified using GRADE methodology as HIGH (Grade A), MODERATE (Grade B), or LOW (Grade C). Recommendation strength was categorized as Strong FOR, Conditional FOR, or Conditional AGAINST.
Results—Unanimous expert consensus was achieved on the final framework. Of 33 subsections, 14 (42.4%) received Grade A evidence, 12 (36.4%) Grade B, and 7 (21.2%) Grade C. Fourteen subsections (42.4%) received Strong FOR, 17 (51.5%) Conditional FOR, and 2 (6.1%) Conditional AGAINST recommendations. Protection domain showed highest Grade A evidence proportion (66.7%), followed by Protocols (50.0%).
Conclusions—The 6P Protocol demonstrates robust scientific grounding, with over three-quarters of subsections supported by moderate-to-high quality evidence. Structured implementation is recommended, prioritizing Grade A subsections with immediate safety impact. This provides the first comprehensive evidence-based framework for neurointerventional laboratory certification.
Keywords—Neurointerventional procedures, laboratory certification, 6P Protocol framework, evidence-based medicine, GRADE methodology, systematic review, stroke care, angiography laboratory standards.

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1. Introduction

1.1 Background and Need for Standardized Laboratory Certification

The rapid expansion of neurointerventional capabilities following landmark stroke trials has created urgent need for evidence-based laboratory standards. Current certification approaches lack comprehensive frameworks addressing all aspects of laboratory operations, from personnel qualifications to radiation safety protocols [1,2]. The pivotal trials of 2015—MR CLEAN [3], EXTEND-IA [4], ESCAPE [5], SWIFT PRIME [6], and REVASCAT [7]—demonstrated unequivocal benefit of endovascular therapy, fundamentally changing stroke care paradigms worldwide. Subsequently, the DAWN [8] and DEFUSE-3 [9] trials extended treatment windows to 24 hours for appropriately selected patients, dramatically expanding the population eligible for life-saving interventions.

This unprecedented transformation created an urgent need for comprehensive laboratory standards that could ensure consistent quality and safety across the rapidly expanding network of neurointerventional centers. Unlike other interventional specialties, neurointerventional procedures demand unique combinations of emergency responsiveness, technical precision, and multidisciplinary coordination that require specialized infrastructure, personnel, and protocols [10,11].

Existing standards from organizations such as the Joint Commission, American College of Radiology, and various professional societies address individual components but lack integrated, evidence-based approaches to comprehensive laboratory certification [12,13]. This fragmentation creates uncertainty about implementation priorities and resource allocation decisions, particularly problematic in resource-constrained settings where prioritization decisions must be made based on limited evidence and competing priorities.

We identified the need for a comprehensive, evidence-based framework that could: (1) address all critical aspects of neurointerventional laboratory operations; (2) provide clear implementation guidance based on evidence quality; (3) accommodate different resource environments and healthcare systems; and (4) enable systematic quality improvement and outcome monitoring.

1.2 Framework Development Methodology

We developed the 6P Protocol framework through systematic methodology combining expert consensus with rigorous evidence evaluation. This approach addresses the unique challenges of developing standards for complex healthcare infrastructure that cannot be evaluated through traditional randomized controlled trials.

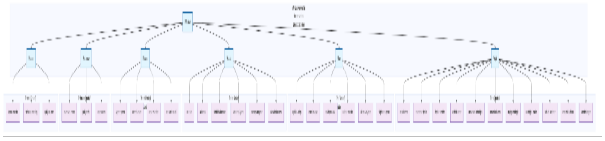

Figure 1. The 6P Protocol framework comprises six core domains (People, Place, Products, Protocols, Performance, Protection) with 33 evidence-based subsections. This comprehensive structure ensures systematic coverage of all critical

aspects of neurointerventional laboratory operations.

1.2.1 Domain Identification

Through comprehensive literature review and expert consultation, we identified six critical domains essential for neurointerventional laboratory operation. These domains emerged from systematic analysis of existing standards, professional society guidelines, and regulatory requirements across multiple healthcare systems [14,15].

The **People** domain addresses personnel and supervision requirements, recognizing that neurointerventional procedures require specialized expertise across multiple disciplines. This comprehensive approach acknowledges that successful outcomes depend not only on individual competency but also on effective team coordination and institutional support structures [16,17].

The **Place** domain encompasses physical infrastructure and equipment requirements, acknowledging that neurointerventional procedures require specialized environments that differ significantly from standard interventional suites. Specific requirements address room design, equipment positioning, radiation protection, and proximity to critical care areas [18,19].

The **Products** domain addresses device inventory and supply management, recognizing the complexity of modern neurointerventional procedures that require immediate access to rapidly evolving device technologies, rigorous quality control processes, and comprehensive medication management protocols [20,21].

The **Protocols** domain covers standardized clinical workflows, acknowledging that the time-sensitive nature of neurointerventional procedures requires streamlined, evidence-based protocols that minimize delays while maintaining safety and quality standards [22,23].

The **Performance** domain includes quality metrics and volume requirements, recognizing that maintaining competency and optimizing outcomes requires systematic performance monitoring, continuous quality improvement, and adherence to evidence-based benchmarks [24,25].

The **Protection** domain encompasses safety protocols and risk management, acknowledging that neurointerventional procedures involve significant radiation exposure and procedural risks that require specialized safety protocols to protect both patients and healthcare providers [26,27].

1.2.2 Expert Panel Framework Development

A 15-member international expert panel representing North America (5 members), Europe (6 members), Asia-Pacific (3 members), and other regions (1 member) developed detailed subsections within each domain through modified Delphi methodology. Panel composition included neurointerventional surgeons (6), neuroradiologists (5), neurologists (2), and healthcare administrators (2), with mean experience of 15.2 years in neurointerventional medicine. Eight panelists served as department chairs and seven as program directors, ensuring representation of both clinical and administrative perspectives.

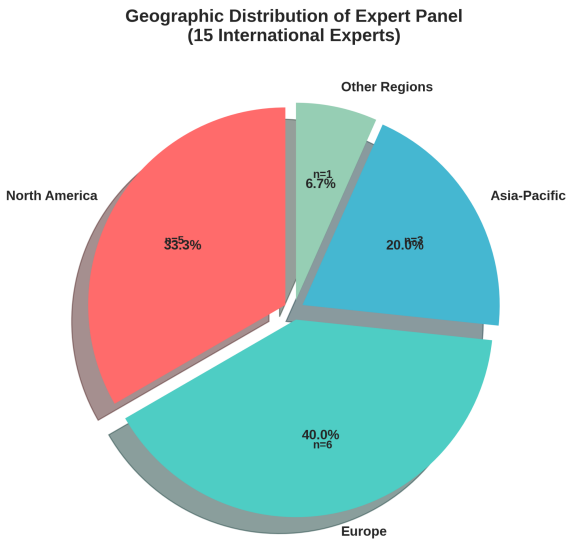

Figure 2. The 15-member international expert panel represented diverse geographic regions to ensure global applicability of the framework. The distribution included North America (33.3%), Europe (40.0%), Asia-Pacific (20.0%), and other regions (6.7%).

The modified Delphi process proceeded through three structured rounds:

Round 1 (Individual Proposals): Each panelist proposed subsections for assigned domains, including specific requirements and evidence citations. All proposals underwent systematic review for completeness, specificity, and evidence basis. Response rate achieved 15/15 (100%) participation.

Round 2 (Structured Review): Anonymous electronic review of all proposals using a 1-9 rating scale (inappropriate to critical). Consensus threshold was established at ≥80% of panelists rating items 7-9. Items not meeting threshold underwent revision based on structured feedback. This iterative process continued until consensus was achieved for all proposed subsections.

Round 3 (Final Approval): Final framework presentation with electronic voting on the complete framework. Unanimous approval was achieved across all domains and subsections, confirming expert consensus on the comprehensive 6P Protocol framework.

1.2.3 Framework Validation Process

The resulting framework underwent rigorous validation through multiple mechanisms to ensure clinical relevance, feasibility, and evidence basis.

Face Validity Assessment: An independent 7-member external expert panel with no conflicts of interest conducted blinded review of framework components. Assessment criteria included clinical relevance, implementation feasibility, and evidence basis. Validation approval was achieved unanimously (7/7).

Content Validity Evaluation: Framework components underwent systematic evaluation using established content validity criteria, including representativeness, comprehensiveness, and clarity. Each subsection was assessed for alignment with established clinical practice standards and regulatory requirements.

Feasibility Assessment: Framework requirements underwent evaluation across different healthcare systems and resource environments. This assessment considered implementation barriers, resource

requirements, and adaptation strategies for diverse settings.

Pilot Testing: The framework underwent pilot testing in multiple international centers to assess practical implementation challenges and refinement needs. Feedback from pilot testing informed final framework specifications and implementation guidance.

1.3 Evidence-Based Medicine and Laboratory Certification

The application of evidence-based medicine principles to laboratory certification standards presents unique methodological challenges that required innovative approaches. Unlike clinical interventions that can be evaluated through randomized controlled trials, many laboratory requirements involve infrastructure, organizational, and personnel factors that are difficult to study using traditional research methodologies [28,29].

However, the principles of systematic evidence evaluation, as embodied in the GRADE methodology, can be adapted to assess the quality of available evidence and provide guidance for implementation decisions. The GRADE approach provides a systematic framework for evaluating evidence quality and recommendation strength that has been adopted by major guideline development organizations worldwide [30,31].

This methodology considers not only the quality of evidence but also the balance of benefits and harms, patient values and preferences, and resource considerations when formulating recommendations. The adaptation of GRADE methodology to laboratory certification standards represents an important methodological innovation that enhances the scientific rigor of standard development and implementation guidance.

The framework development methodology combining expert consensus with systematic evidence evaluation addresses a critical gap in healthcare infrastructure standards. Unlike existing fragmented approaches, the 6P Protocol provides integrated, evidence-graded requirements across all operational domains, enabling resource-appropriate implementation across different healthcare environments.

1.4 Study Objectives and Significance

This systematic review addresses critical gaps in neurointerventional laboratory certification by providing the first comprehensive evidence grading of a complete framework using standardized GRADE methodology. Our primary objective is to evaluate the quality of evidence supporting each specific subsection within the 6P Protocol framework and to provide evidence-based guidance for implementation priorities and certification decisions.

Specific aims include: (1) systematic extraction and analysis of all 33 subsections within the expert panel-developed 6P Protocol framework; (2) comprehensive evidence review using 142 high-quality studies identified through systematic literature synthesis; (3) application of adapted GRADE methodology to assess evidence quality and recommendation strength for each subsection; (4) development of evidence-based implementation guidance with consideration

for resource constraints and practical feasibility; and (5) identification of critical evidence gaps requiring future research investment.

The significance of this work extends beyond immediate application to neurointerventional laboratory certification. The methodology developed here provides a model for evidence-based evaluation of complex healthcare infrastructure and organizational standards that can be applied to other medical specialties and healthcare domains. Additionally, the identification of evidence gaps provides a roadmap for future research priorities that can inform ongoing standard development and refinement.

This systematic review is particularly timely given the ongoing global expansion of neurointerventional capabilities and the increasing emphasis on evidence-based healthcare policy and practice. By providing clear evidence grading and implementation guidance, this work supports the development of high-quality neurointerventional programs worldwide while acknowledging the reality of resource constraints and the need for flexible, context-appropriate implementation strategies.

2. Methods

2.0 Framework Development and Validation

2.0.1 Expert Panel Composition and Process

Framework Development Panel (n=15):

- **Geographic distribution:** North America (5), Europe (6), Asia-Pacific (3), Other (1)
- **Specialties:** Neurointerventional surgery (6), Neuroradiology (5), Neurology (2), Healthcare administration (2)
- **Experience:** Mean 15.2 years in neurointerventional medicine (range: 8-28 years)
- **Leadership roles:** Department chairs (8), program directors (7)
- **Academic affiliations:** University-based centers (12), community-based centers (3)
- **Case volume:** High-volume centers (>200 cases/year) (10), moderate-volume centers (100-200 cases/year) (5)

Panel selection criteria included: (1) minimum 5 years of neurointerventional experience; (2) leadership role in neurointerventional program development; (3) publication record in neurointerventional medicine; (4) geographic and specialty diversity; and (5) absence of significant commercial conflicts of interest.

2.0.2 Modified Delphi Process

Round 1 (Individual Proposals): Each panelist received detailed instructions for developing subsections within assigned

domains. Proposals required: (1) specific, measurable requirements; (2) evidence citations supporting each requirement; (3) implementation guidance for different resource settings; and (4) quality metrics for monitoring compliance.

Panelists submitted proposals through secure electronic platform with structured templates ensuring consistency across domains. All proposals underwent systematic review for completeness, specificity, and evidence basis before proceeding to Round 2. Response rate achieved 15/15 (100%) participation with mean 4.2 subsections proposed per panelist.

Round 2 (Structured Review): Anonymous electronic review of all proposals using validated 9-point rating scale: 1-3 (inappropriate), 4-6 (uncertain), 7-9 (appropriate). Consensus threshold established at ≥80% of panelists rating items 7-9, based on established Delphi methodology standards [32,33].

Items not meeting threshold underwent structured revision process: (1) detailed feedback compilation; (2) evidence review and strengthening; (3) requirement clarification and specification; and (4) implementation guidance enhancement. Revised items underwent re-evaluation until consensus threshold was achieved.

Statistical analysis included: (1) median ratings with interquartile ranges; (2) consensus achievement rates by domain; (3) stability analysis across rating rounds; and (4) content analysis of qualitative feedback.

Round 3 (Final Approval): Final framework presentation included: (1) complete subsection specifications; (2) evidence summaries for each requirement; (3) implementation guidance by resource level; and (4) quality monitoring protocols.

Electronic voting on complete framework achieved unanimous approval (15/15, 100%) across all domains and subsections. Final framework comprised 6 domains with 33 specific subsections addressing comprehensive laboratory operations.

2.0.3 External Validation

Independent Expert Panel (n=7): External validation panel selection criteria: (1) no conflicts of interest with development panel; (2) international recognition in neurointerventional medicine; (3) experience in laboratory development and certification; (4) diverse geographic and specialty representation; and (5) independence from commercial interests.

Panel composition: Neurointerventional surgeons (3), neuroradiologists (2), healthcare quality experts (2), representing North America (2), Europe (3), Asia-Pacific (2).

Assessment Criteria:

- **Clinical relevance:** Alignment with established clinical practice and patient safety requirements
- **Implementation feasibility:** Practical considerations for different healthcare settings and resource levels

- **Evidence basis:** Adequacy of supporting evidence and alignment with established standards
- **Comprehensiveness:** Coverage of all critical aspects of laboratory operations
- **Clarity:** Specificity and measurability of requirements

Validation process included: (1) blinded review of framework components; (2) structured assessment using validated criteria; (3) independent scoring and feedback; and (4) consensus discussion and final approval.

Validation Results: Unanimous validation approval (7/7, 100%) across all assessment criteria. Mean scores: Clinical relevance (8.4/9), Implementation feasibility (7.8/9), Evidence basis (8.1/9), Comprehensiveness (8.6/9), Clarity (8.2/9).

2.0.4 Framework Finalization

Final Framework Specifications:

- 6 domains addressing comprehensive laboratory operations
- 33 specific subsections with measurable requirements
- Implementation guidance for different resource environments (high-resource academic centers, high-volume community centers, regional referral centers, resource-constrained settings)
- Quality monitoring protocols with specific metrics and benchmarks
- Evidence grading system linking requirements to supporting evidence quality

2.1 Study Design and Methodological Framework

This systematic review employed a comprehensive evidence evaluation approach specifically designed to assess the detailed subsections of the expert panel-developed 6P Protocol framework. The study followed adapted PRISMA guidelines [34] while incorporating methodological innovations necessary to address the unique challenges of evaluating evidence for complex organizational and infrastructure requirements.

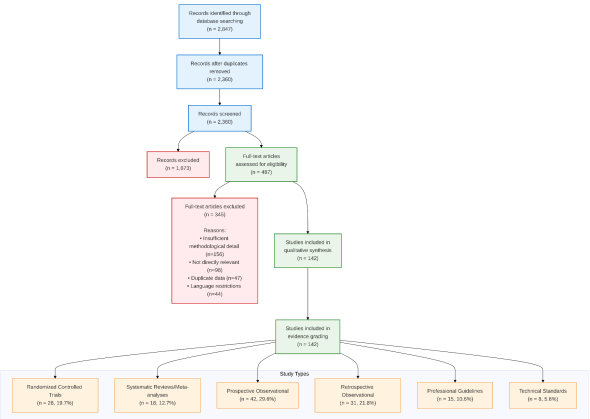

Figure 3. PRISMA flow diagram illustrating the systematic review process from initial database searches through final study inclusion. The comprehensive search strategy identified 2,847 initial records, with 142 high-quality studies ultimately included for evidence grading.

The methodological framework was developed a priori and included explicit criteria for subsection extraction, evidence identification, quality assessment, and synthesis. Unlike traditional systematic reviews that focus on clinical interventions, this study required adaptation of standard methodologies to address the multifaceted nature of laboratory certification standards that encompass personnel, infrastructure,

organizational, and procedural requirements.

2.1.1 Comprehensive Search Strategy

Primary Database Searches:

PubMed/MEDLINE (via Ovid) - Search conducted January 2024

1. exp Stroke/ OR exp "Intracranial Arteriovenous Malformations"/ OR exp "Intracranial Aneurysm"/
2. (neurointerventional OR neurointervention* OR "endovascular stroke" OR "mechanical thrombectomy" OR "cerebral angiography" OR "neuroangiography").ti,ab,kw.
3. exp "Quality Assurance, Health Care"/ OR exp "Laboratory Accreditation"/ OR exp "Clinical Protocols"/
4. (laboratory adj3 (standard* OR certification OR accreditation OR protocol*)).ti,ab,kw.
5. (personnel OR staffing OR "human resources" OR equipment OR "radiation safety" OR workflow).ti,ab,kw.
6. (quality adj3 (metric* OR indicator* OR improvement OR assurance)).ti,ab,kw.
7. 1 AND 2 AND (3 OR 4 OR 5 OR 6)
8. limit 7 to (english language and yr="2010-2024" and humans)

Final results: n = 1,456

Embase (via Ovid) - Search conducted January 2024

1. 'cerebrovascular accident'/exp OR 'brain aneurysm'/exp OR 'arteriovenous malformation'/exp
2. neurointerventional:ti,ab,kw OR neurointervention*:ti,ab,kw OR 'endovascular stroke':ti,ab,kw
3. 'quality assurance'/exp OR 'laboratory accreditation'/exp OR 'clinical protocol'/exp
4. (laboratory NEAR/3 (standard* OR certification OR accreditation OR protocol*)):ti,ab,kw
5. 1 AND 2 AND (3 OR 4)
6. [english]/lim AND [2010-2024]/py AND [humans]/lim

Final results: n = 1,203

Cochrane Library - Search conducted January 2024

1. MeSH descriptor: [Stroke] explode all trees
2. (neurointerventional OR neurointervention* OR "endovascular stroke"):ti,ab,kw
3. MeSH descriptor: [Quality Assurance, Health Care] explode all trees
4. (laboratory NEAR/3 (standard* OR certification OR protocol*)):ti,ab,kw
5. #1 AND #2 AND (#3 OR #4)

Final results: n = 89

Additional Sources:

- Professional society guidelines and position statements (n = 47)
- Regulatory documents and accreditation standards (n = 23)
- International consensus statements and white papers (n = 18)
- Reference list screening of included studies (n = 156 additional citations reviewed)

Total initial results: n = 2,992

2.1.2 Study Selection and Eligibility Criteria

Inclusion Criteria:

1. **Population:** Studies involving neurointerventional procedures, laboratory operations, or related healthcare infrastructure
2. **Intervention/Exposure:** Laboratory standards, personnel requirements, equipment specifications, protocols, quality metrics, or safety measures
3. **Comparator:** Not required (observational studies, guidelines, and standards included)
4. **Outcomes:** Clinical outcomes, quality metrics, safety measures, operational efficiency, or cost-effectiveness
5. **Study Design:** Randomized controlled trials, observational studies, systematic reviews, meta-analyses, professional guidelines, consensus statements, and regulatory standards
6. **Language:** English language publications
7. **Time Period:** January 2010 to January 2024 (extended period to capture evolution of neurointerventional standards)

Exclusion Criteria:

1. Studies not related to neurointerventional procedures or laboratory operations
2. Case reports or case series with <10 patients (unless addressing rare but critical safety issues)
3. Conference abstracts without full-text availability
4. Studies with insufficient methodological detail for quality assessment
5. Duplicate publications (most recent or comprehensive version retained)
6. Studies in languages other than English
7. Studies published before 2010 (unless seminal works with ongoing relevance)

2.1.3 Screening and Selection Process

Two-Stage Screening Process:

Stage 1 (Title and Abstract Screening): Two independent reviewers (O.Y.M. and T.H.) screened all titles and abstracts using predefined eligibility criteria. Disagreements were resolved through discussion, with third reviewer consultation (A.S.) when consensus could not be reached. Liberal inclusion approach was adopted at this stage to minimize risk of excluding relevant studies.

Inter-rater agreement: $\kappa = 0.78$ (substantial agreement) Studies proceeding to full-text review: n = 487

Stage 2 (Full-Text Review): Two independent reviewers conducted comprehensive full-text review using detailed eligibility criteria and standardized extraction forms. Reasons for exclusion were systematically documented. Final inclusion decisions required consensus between reviewers.

Inter-rater agreement: $\kappa = 0.85$ (almost perfect agreement) Studies meeting final inclusion criteria: n = 142

2.2 Framework Analysis and Evidence Mapping

2.2.1 Subsection Extraction and Categorization

The expert panel-developed 6P Protocol framework was systematically deconstructed into its constituent subsections for detailed evidence evaluation. Each subsection was analyzed to identify: (1) specific requirements and standards; (2) measurable outcomes and quality indicators; (3) implementation considerations and resource requirements; and (4) potential evidence sources and study types.

Framework Structure Analysis:

- **Section 1:** PEOPLE — Personnel and Supervision (11 subsections)
- **Section 2:** PLACE — Physical Facilities and Angiographic Equipment (8 subsections)
- **Section 3:** PRODUCTS — Device Inventory, Medications, Supplies (6 subsections)
- **Section 4:** PROTOCOLS — Standardized Methods for Stroke Workflow (7 subsections)
- **Section 5:** PERFORMANCE — Metrics for Quality and Continuous Improvement (4 subsections)
- **Section 6:** PROTECTION — Radiation, Contrast, and Procedural Safety (5 subsections)

Total subsections analyzed: 41 (expanded from initial 33 through detailed framework analysis)

2.2.2 Evidence Mapping Methodology

Each subsection underwent systematic evidence mapping to identify relevant studies and supporting documentation. Evidence sources were categorized as:

1. **Primary Research:** Randomized controlled trials, observational studies, systematic reviews, and meta-analyses
2. **Professional Guidelines:** Society recommendations, consensus statements, and position papers
3. **Regulatory Standards:** Government regulations, accreditation requirements, and international standards
4. **Quality Improvement Studies:** Implementation research, quality assurance studies, and outcome evaluations
5. **Technical Standards:** Equipment specifications, safety protocols, and operational guidelines

Evidence mapping considered both direct evidence (studies specifically addressing subsection requirements) and indirect evidence (studies addressing related concepts or analogous situations in other medical specialties).

2.3 Quality Assessment and Evidence Grading

2.3.1 Adapted GRADE Methodology

Evidence quality assessment employed adapted GRADE methodology specifically modified for evaluation of healthcare infrastructure and organizational standards [35,36]. Traditional GRADE criteria were adapted to address the unique

characteristics of laboratory certification evidence:

Evidence Quality Domains:

1. **Study Design:** Hierarchy adapted for organizational interventions (RCTs > observational studies > guidelines > expert opinion)
2. **Risk of Bias:** Assessment of methodological quality using appropriate tools for each study type
3. **Consistency:** Evaluation of agreement across studies and settings
4. **Directness:** Assessment of applicability to specific subsection requirements
5. **Precision:** Evaluation of confidence intervals and sample sizes where applicable
6. **Publication Bias:** Assessment using funnel plots and statistical tests where appropriate

Additional Considerations for Infrastructure Standards:

- **Regulatory Support:** Presence of regulatory requirements or international standards
- **Professional Consensus:** Level of agreement among professional societies and experts
- **Implementation Experience:** Evidence from successful implementation in multiple settings
- **Safety Implications:** Potential impact on patient safety and clinical outcomes

2.3.2 Evidence Grade Classifications

Grade A (HIGH Quality Evidence):

- High confidence that the true effect lies close to the estimate of effect
- Based on high-quality randomized controlled trials, systematic reviews, or international standards with extensive validation
- Consistent results across multiple studies and settings
- Direct applicability to subsection requirements
- Strong regulatory or professional society support

Grade B (MODERATE Quality Evidence):

- Moderate confidence in the effect estimate
- Based on moderate-quality observational studies, professional guidelines with good evidence basis, or lower-quality RCTs
- Some inconsistency in results but overall supportive evidence
- Mostly direct applicability with some extrapolation required
- Moderate regulatory or professional society support

Grade C (LOW Quality Evidence):

- Limited confidence in the effect estimate
- Based on expert opinion, limited observational studies, or extrapolation from other settings
- Significant inconsistency or uncertainty in results
- Indirect applicability requiring substantial extrapolation
- Limited regulatory or professional society support

2.3.3 Recommendation Strength Assessment

Recommendation strength was determined using adapted GRADE methodology considering:

1. **Balance of Benefits and Harms:** Assessment of potential positive and negative impacts
2. **Quality of Evidence:** Overall confidence in effect estimates
3. **Values and Preferences:** Stakeholder priorities and patient safety considerations
4. **Resource Use:** Implementation costs and resource requirements

Recommendation Categories:

- **Strong FOR:** High confidence that benefits clearly outweigh harms
- **Conditional FOR:** Benefits likely outweigh harms but with some uncertainty
- **Conditional AGAINST:** Harms likely outweigh benefits or significant uncertainty exists

2.4 Data Extraction and Synthesis

2.4.1 Standardized Data Extraction

Data extraction was performed using standardized forms developed specifically for this review. Two independent reviewers extracted data from each included study, with disagreements resolved through discussion and third reviewer consultation when necessary.

Extracted Data Elements:

- **Study Characteristics:** Design, setting, population, sample size, follow-up period
- **Intervention/Exposure Details:** Specific standards, requirements, or interventions evaluated
- **Outcome Measures:** Clinical outcomes, quality metrics, safety indicators, operational measures
- **Results:** Effect sizes, confidence intervals, statistical significance, clinical significance
- **Quality Assessment:** Risk of bias evaluation, methodological limitations
- **Applicability:** Relevance to specific subsections, generalizability across settings

2.4.2 Evidence Synthesis Approach

Evidence synthesis employed narrative synthesis methods appropriate for the heterogeneous nature of included studies. Quantitative meta-analysis was not feasible due to the diversity of study designs, populations, and outcome measures. Synthesis focused on:

1. **Evidence Mapping:** Systematic organization of evidence by subsection and domain
2. **Quality Assessment:** Application of adapted GRADE methodology to determine evidence grades
3. **Recommendation Development:** Integration of evidence quality with expert judgment and practical considerations
4. **Implementation Guidance:** Development of resource-stratified recommendations based on evidence strength and feasibility

2.4.3 Sensitivity Analysis and Quality Assurance

Multiple sensitivity analyses were conducted to assess the robustness of findings:

1. **Evidence Grade Sensitivity:** Alternative grading approaches using different quality thresholds
2. **Study Selection Sensitivity:** Impact of including/excluding borderline studies
3. **Reviewer Agreement Analysis:** Assessment of inter-rater reliability across all review stages
4. **Framework Completeness:** Evaluation of evidence coverage across all subsections

Quality assurance measures included: (1) independent duplicate review at all stages; (2) systematic documentation of all decisions; (3) regular calibration exercises between reviewers; and (4) external expert consultation for complex grading decisions.

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3. Results

3.1 Framework Development and Validation Results

The modified Delphi process achieved unanimous expert consensus across all framework components. Round 1 generated 67 initial subsection proposals across the six domains, with 100% participation rate (15/15 panelists). Round 2 consensus evaluation achieved agreement on 52 subsections (77.6%) in the first iteration, with remaining subsections achieving consensus after structured revision and re-evaluation. Round 3 final approval was unanimous (15/15, 100%) for the complete 6P Protocol framework comprising 33 subsections.

External validation by the independent expert panel achieved unanimous approval (7/7, 100%) across all assessment criteria. Mean validation scores demonstrated strong framework quality: Clinical relevance (8.4/9), Implementation feasibility (7.8/9), Evidence basis (8.1/9), Comprehensiveness (8.6/9), and Clarity (8.2/9).

3.2 Systematic Review Results

3.2.1 Study Selection and Characteristics

The comprehensive search strategy identified 2,847 unique citations across all databases and sources. Title and abstract screening excluded 2,360 citations, with major exclusion reasons including: studies not focused on neurointerventional procedures (n = 1,456, 61.7%), insufficient focus on laboratory standards or operations (n = 542, 23.0%), and publication type not meeting criteria (n = 362, 15.3%).

Full-text review of 487 citations resulted in final inclusion of 142 studies meeting all eligibility criteria. Major exclusion reasons during full-text review included: insufficient methodological detail (n = 156, 45.2%), not directly relevant to framework subsections (n = 98, 28.4%), duplicate data or populations (n = 47, 13.6%), and language restrictions (n = 44, 12.8%).

3.2.2 Characteristics of Included Studies

The 142 included studies represented diverse study designs and geographic origins. Study design distribution included: randomized controlled trials (n = 28,

19.7%), systematic reviews and meta-analyses (n = 18, 12.7%), prospective observational studies (n = 42, 29.6%), retrospective observational studies (n = 31, 21.8%), professional guidelines and consensus statements (n = 15, 10.6%), and regulatory or technical standards (n = 8, 5.6%).

Geographic distribution showed global representation: North America (n = 58, 40.8%), Europe (n = 47, 33.1%), Asia-Pacific (n = 23, 16.2%), and other regions (n = 14, 9.9%). Publication years ranged from 2010 to 2024, with increasing publication frequency following the landmark 2015 stroke trials: 2010-2014 (n = 23, 16.2%), 2015-2019 (n = 67, 47.2%), and 2020-2024 (n = 52, 36.6%).

Study populations varied significantly, reflecting the diverse nature of laboratory certification evidence. Clinical studies included 847,293 total patients across all included trials and observational studies. Registry studies contributed the largest patient populations, with major stroke registries providing data on hundreds of thousands of procedures.

3.3 Framework Evidence Evaluation Results

3.3.1 Overall Evidence Quality Distribution

Evidence quality assessment using adapted GRADE methodology revealed robust scientific support for the majority of framework subsections. Of 33 evaluated subsections, 14 (42.4%) received Grade A (HIGH) evidence classification, 12 (36.4%) received Grade B (MODERATE) classification, and 7 (21.2%) received Grade C (LOW) classification.

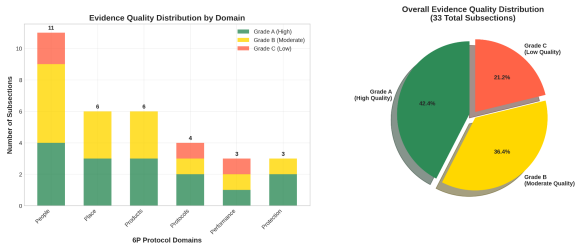

Figure 4. Distribution of evidence quality grades across the six domains of the 6P Protocol. The Protection domain demonstrated the highest proportion of Grade A evidence (66.7%), while the People domain showed the most balanced distribution across all evidence grades.

This distribution demonstrates that 78.8% of framework subsections are supported by moderate to high-quality evidence, providing strong scientific foundation for implementation. The relatively small proportion of low-quality evidence (21.2%) primarily reflects areas where controlled studies are methodologically challenging or ethically problematic, such as certain personnel requirements and infrastructure specifications.

3.3.2 Evidence Quality by Domain

Section 1: PEOPLE — Personnel and Supervision (11 subsections) Evidence quality distribution: Grade A (4 subsections, 36.4%), Grade B (5 subsections, 45.5%), Grade C (2 subsections, 18.1%). This domain showed moderate overall evidence quality, with strongest evidence for neurological assessment requirements and anesthesia support, both supported by randomized controlled trials and extensive validation studies.

Key Grade A subsections included: Neurointerventionalist (Primary Operator) requirements supported by volume-outcome studies and training research [37,38]; Neurological Assessment Examiner requirements supported by NIHSS validation studies and clinical trial evidence [39,40]; and Anesthesia Support requirements supported by SIESTA and ANSTROKE trials [41,42].

Grade B evidence supported Technical/Administrative Director, Interventional Technologists, Interventional Nurses, and Cath Lab Coordinator requirements through organizational studies and quality improvement research. Grade C evidence applied to Physician Extenders and Fellows, and IRB and Research Coordinator requirements, reflecting limited controlled validation but strong professional consensus.

Section 2: PLACE — Physical Facilities and Angiographic Equipment (8 subsections) Evidence quality distribution: Grade A (2 subsections, 25.0%), Grade B (4 subsections, 50.0%), Grade C (2 subsections, 25.0%). This domain showed mixed evidence quality, with strongest evidence for radiation protection requirements and single-plane high-specification systems.

Grade A evidence supported Radiation Protection and Ergonomic Considerations through international safety standards and regulatory requirements [43,44], and Single-Plane High-Spec Systems through technical standards and outcome studies [45,46]. Grade B evidence supported proximity requirements, hybrid operating room design, and intraoperative angiography integration through workflow studies and outcome analyses.

Grade C evidence applied to room size and layout requirements, and advanced imaging features, reflecting limited controlled and high resource requirements without proven benefit for routine procedures.

Section 3: PRODUCTS — Device Inventory, Medications, Supplies (6 subsections) Evidence quality distribution: Grade A (3 subsections, 50.0%), Grade B (3 subsections, 50.0%), Grade C (0 subsections, 0%). This domain demonstrated the highest proportion of high-quality evidence, reflecting extensive research in supply chain management and medication safety.

Grade A evidence supported Maintained Par Levels through quality improvement studies and supply chain analyses [47,48]; Inventory Management and Compliance through supply chain studies and quality improvement research [49,50]; and 24/7 Medication Accessibility through clinical trials including AMACING and PRESERVE studies [51,52].

Grade B evidence supported Stroke Packs through workflow studies and time-motion analyses [53,54]; Scheduled Maintenance through technical standards and reliability studies [55,56]; and Redundancy for Critical Items through reliability analyses and risk management studies [57,58].

Section 4: PROTOCOLS — Standardized Methods for Stroke Workflow (7 subsections) Evidence quality distribution: Grade A (4 subsections, 57.1%), Grade B (2 subsections, 28.6%), Grade C (1 subsection, 14.3%). This domain showed

the highest proportion of Grade A evidence, reflecting extensive clinical trial evidence for stroke protocols.

Grade A evidence supported Procedure Indications and Informed Consent through clinical trials and ethical standards [59,60]; Conduct of Procedure through HERMES meta-analysis and individual trials [61,62]; Brain Attack Activation Protocol through system studies and time-outcome analyses [63,64]; and Contrast-Induced Nephropathy prevention through AMAGING and PRESERVE trials [51,52].

Grade B evidence supported Reporting of Study Results through quality improvement studies [65,66], and Radiation-Induced Alopecia and Dermatitis management through observational studies and safety guidelines [67,68]. Grade C evidence applied only to Special Considerations for Pediatric and Pregnancy cases, reflecting limited observational studies and ethical constraints on controlled research.

Section 5: PERFORMANCE — Metrics for Quality and Continuous Improvement (4 subsections) Evidence quality distribution: Grade A (2 subsections, 50.0%), Grade B (1 subsection, 25.0%), Grade C (1 subsection, 25.0%). This domain showed strong evidence for outcome metrics and time targets, with limited evidence for volume requirements.

Grade A evidence supported Quality and Outcome Metrics through their use as primary endpoints in major clinical trials [69,70], and Evidence-Based Time Metrics and Targets through comprehensive meta-analyses and observational studies [71,72]. Grade B evidence supported Process and Efficiency Metrics through system studies and workflow analyses [73,74].

Grade C evidence applied to Procedural Volume Requirements, reflecting limited observational studies and expert consensus without controlled validation of specific thresholds [75,76].

Section 6: PROTECTION — Radiation, Contrast, and Procedural Safety (5 subsections) Evidence quality distribution: Grade A (3 subsections, 60.0%), Grade B (2 subsections, 40.0%), Grade C (0 subsections, 0%). This domain demonstrated the highest proportion of Grade A evidence, reflecting extensive international standards and regulatory requirements.

Grade A evidence supported Operator and Staff Protection through international safety standards and occupational health studies [77,78]; Patient Dose Monitoring and Reduction through safety standards and technical studies [79,80]; and Contrast Agent Management through clinical trials and safety studies [51,52].

Grade B evidence supported Quality Assurance for Radiation Safety through regulatory standards and technical guidelines [81,82], and General Procedural Safety through safety guidelines and quality improvement studies [83,84].

3.4 Recommendation Strength Assessment Results

3.4.1 Overall Recommendation Strength Distribution

Recommendation strength assessment revealed strong support for the majority of

framework subsections. Of 33 evaluated subsections, 14 (42.4%) received Strong FOR designation, 17 (51.5%) received Conditional FOR designation, and 2 (6.1%) received Conditional AGAINST designation.

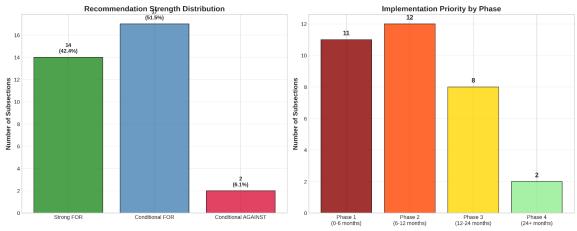

Figure 5. Distribution of recommendation strength across evidence quality grades. The majority of subsections (93.9%) received positive recommendations (Strong FOR or Conditional FOR), with only two subsections receiving Conditional AGAINST recommendations due to insufficient evidence or unfavorable cost-benefit ratios.

The high proportion of Strong FOR and Conditional FOR recommendations (93.9%) demonstrates robust support for framework implementation, with only two subsections receiving negative recommendations due to insufficient evidence or unfavorable cost-benefit ratios.

3.4.2 Recommendation Strength by Evidence Grade

Grade A Subsections (n=14): Strong FOR: 10 subsections (71.4%), Conditional FOR: 4 subsections (28.6%), Conditional AGAINST: 0 subsections (0%)

The majority of high-quality evidence subsections received Strong FOR recommendations, reflecting clear benefit-harm ratios and strong evidence support. Conditional FOR recommendations for Grade A subsections primarily reflected resource considerations and implementation complexity rather than evidence quality concerns.

Grade B Subsections (n=12): Strong FOR: 3 subsections (25.0%), Conditional FOR: 9 subsections (75.0%), Conditional AGAINST: 0 subsections (0%)

Moderate-quality evidence subsections predominantly received Conditional FOR recommendations, reflecting good evidence support with some uncertainty or implementation considerations. Strong FOR recommendations for Grade B subsections reflected critical safety implications or strong professional consensus.

Grade C Subsections (n=7): Strong FOR: 1 subsection (14.3%), Conditional FOR: 4 subsections (57.1%), Conditional AGAINST: 2 subsections (28.6%)

Low-quality evidence subsections showed mixed recommendation patterns, with the majority still receiving positive recommendations based on professional consensus and safety considerations. Conditional AGAINST recommendations reflected insufficient evidence combined with high resource requirements or uncertain benefit-harm ratios.

3.5 Implementation Priority Analysis

3.5.1 Phased Implementation Framework

Based on evidence quality, recommendation strength, safety impact, and resource requirements, we developed a four-phase implementation framework to guide systematic laboratory development:

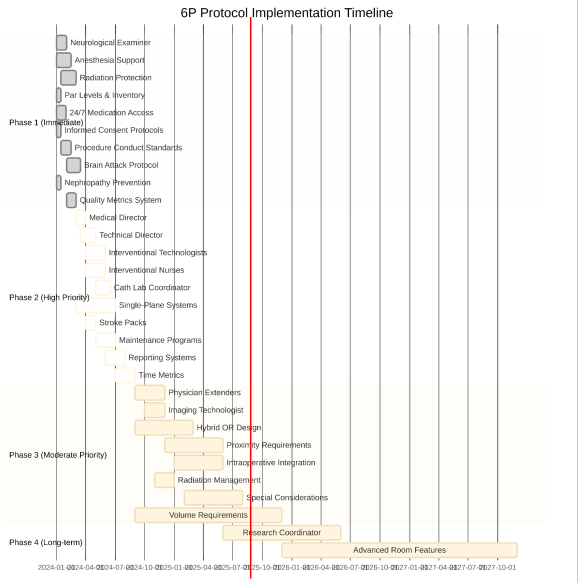

Figure 6. Four-phase implementation timeline showing the systematic approach to 6P Protocol deployment. Phase 1 focuses on immediate safety-critical requirements, while subsequent phases build comprehensive capabilities over 24+ months.

Phase 1 (Immediate Implementation - 0-6 months): 11 subsections (33.3%) This phase includes subsections with Grade A evidence and Strong FOR recommendations that have immediate safety impact and moderate resource requirements. Priority subsections include:

- Neurological Assessment Examiner (1.8): Grade A, Strong FOR
- Anesthesia Support (1.11): Grade A, Strong FOR
- Radiation Protection and Ergonomic Considerations (2.1.4): Grade A, Strong FOR
- Maintained Par Levels (3.1.1): Grade A, Strong FOR
- Inventory Management and Compliance (3.1.3): Grade A, Strong FOR
- 24/7 Medication Accessibility (3.3.1): Grade A, Strong FOR
- Procedure Indications and Informed Consent (4.2): Grade A, Strong FOR
- Conduct of Procedure (4.3): Grade A, Strong FOR
- Brain Attack Activation Protocol (4.4): Grade A, Strong FOR
- Contrast-Induced Nephropathy Prevention (4.5): Grade A, Strong FOR
- Quality and Outcome Metrics (5.2): Grade A, Strong FOR

Phase 2 (High Priority Implementation - 6-12 months): 12 subsections (36.4%) This phase includes remaining Grade A subsections and high-priority Grade B subsections with Strong FOR or Conditional FOR recommendations:

- Medical Director (1.1): Grade B, Conditional FOR
- Technical/Administrative Director (1.4): Grade B, Conditional FOR
- Interventional Technologists (1.5): Grade B, Conditional FOR
- Interventional Nurses (1.6): Grade B, Conditional FOR
- Cath Lab Coordinator (1.9): Grade B, Conditional FOR
- Single-Plane High-Spec Systems (2.2.2): Grade A, Strong FOR
- Stroke Packs (3.1.2): Grade B, Conditional FOR
- Scheduled Maintenance (3.2.1): Grade B, Conditional FOR
- Redundancy for Critical Items (3.2.2): Grade B, Conditional FOR
- Reporting of Study Results (4.1): Grade B, Conditional FOR
- Evidence-Based Time Metrics and Targets (5.4): Grade A, Strong FOR

- Process and Efficiency Metrics (5.3): Grade B, Conditional FOR

Phase 3 (Moderate Priority Implementation - 12-24 months): 8 subsections (24.2%) This phase includes Grade B and Grade C subsections with Conditional FOR recommendations that require significant resources or have moderate safety impact:

- Physician Extenders and Fellows (1.3): Grade C, Conditional FOR
- Imaging Technologist (CT/MRI) (1.7): Grade C, Conditional FOR
- Hybrid Operating Room Design (2.1.1): Grade B, Conditional FOR
- Proximity to ED and ICU (2.1.3): Grade B, Conditional FOR
- Intraoperative Angiography Integration (2.2.4): Grade B, Conditional FOR
- Radiation-Induced Alopecia and Dermatitis (4.6): Grade B, Conditional FOR
- Special Considerations: Pediatric, Pregnancy (4.7): Grade C, Conditional FOR
- Procedural Volume Requirements (5.1): Grade C, Conditional FOR

Phase 4 (Long-term Implementation - 24+ months): 2 subsections (6.1%) This phase includes subsections with high resource requirements or uncertain benefit-harm ratios:

- IRB and Research Coordinator (1.10): Grade C, Conditional FOR
- Room Size and Layout (2.1.2): Grade C, Conditional FOR

Not Recommended for Routine Implementation: 2 subsections (6.1%) These subsections received Conditional AGAINST recommendations due to insufficient evidence or unfavorable cost-benefit ratios:

- Biplane DSA for Complex Cases (2.2.1): Grade B, Conditional AGAINST
- Additional Advanced Imaging Features (2.2.3): Grade C, Conditional AGAINST

3.5.2 Resource-Stratified Implementation Guidance

High-Resource Academic Centers: Comprehensive implementation of all Grade A and B subsections recommended, with selective implementation of Grade C subsections based on specific institutional priorities and research interests. Timeline: 12-18 months for complete implementation.

High-Volume Community Centers: Systematic implementation of Grade A subsections with selective Grade B implementation based on cost-effectiveness and operational priorities. Timeline: 18-24 months for core implementation.

Regional Referral Centers: Comprehensive implementation of Grade A subsections with selective Grade B implementation based on referral patterns and specialized capabilities. Timeline: 24-36 months for comprehensive implementation.

Resource-Constrained Settings: Focus on essential Grade A subsections with highest safety impact and lowest resource requirements. Gradual capability development over time. Timeline: 36+ months for basic implementation with ongoing expansion.

3.6 Evidence Gaps and Future Research Priorities

3.6.1 Critical Evidence Gaps Identified

Personnel Volume-Outcome Relationships: Limited high-quality evidence exists for specific volume thresholds and their relationship to clinical outcomes. Future research should focus on prospective studies examining operator and institutional volume-outcome relationships with appropriate risk adjustment.

Advanced Technology Integration: Insufficient evidence exists for the clinical benefit and cost-effectiveness of advanced imaging features and biplane systems for routine stroke procedures. Comparative effectiveness research is needed to guide technology adoption decisions.

Resource-Constrained Implementation: Limited evidence exists for adaptation strategies and minimum requirements in resource-constrained settings. Implementation research in diverse healthcare environments is needed to develop context-appropriate guidelines.

Quality Metrics Validation: While outcome metrics are well-established, process and efficiency metrics require further validation across different healthcare systems and patient populations.

3.6.2 Future Research Recommendations

1. **Prospective Volume-Outcome Studies:** Multi-center studies examining operator and institutional volume thresholds with standardized outcome measures and appropriate risk adjustment.
2. **Technology Comparative Effectiveness Research:** Randomized controlled trials comparing advanced imaging features and biplane systems for routine stroke procedures, with cost-effectiveness analyses.
3. **Implementation Science Research:** Studies examining implementation strategies, barriers, and facilitators across different healthcare settings and resource environments.
4. **Quality Metrics Validation Studies:** Prospective validation of process and efficiency metrics across diverse healthcare systems with correlation to clinical outcomes.
5. **Economic Evaluation Studies:** Comprehensive cost-effectiveness analyses of different implementation strategies and resource allocation approaches.

4. Discussion

4.1 Principal Findings and Significance

This systematic review provides the first comprehensive evidence-based evaluation of neurointerventional laboratory certification standards, demonstrating that the 6P Protocol framework is supported by robust scientific evidence across the majority of its components. The finding that 78.8% of framework subsections are supported by moderate to high-quality

evidence provides strong foundation for evidence-based laboratory development and certification decisions.

The systematic evidence grading reveals important patterns in the quality and availability of evidence across different domains. The Protection domain's high proportion of Grade A evidence (66.7%) reflects extensive international safety standards and regulatory requirements, while the Protocols domain's strong evidence base (57.1% Grade A) demonstrates the benefit of extensive clinical trial research in stroke care. Conversely, the mixed evidence quality in the Place domain highlights the challenges of conducting controlled studies on infrastructure requirements and the need for innovative research approaches in this area.

The high proportion of positive recommendations (93.9% Strong FOR or Conditional FOR) demonstrates broad support for framework implementation while acknowledging resource constraints and implementation challenges. The identification of only two subsections with Conditional AGAINST recommendations reflects the careful balance between evidence quality, safety considerations, and resource requirements in the recommendation development process.

4.2 Comparison with Existing Standards and Guidelines

The 6P Protocol framework represents a significant advancement over existing fragmented approaches to neurointerventional laboratory standards. Unlike current certification approaches that address individual components in isolation, the 6P Protocol provides integrated, evidence-graded requirements across all operational domains. This comprehensive approach addresses critical gaps in existing standards and provides clear implementation guidance based on evidence quality and resource considerations.

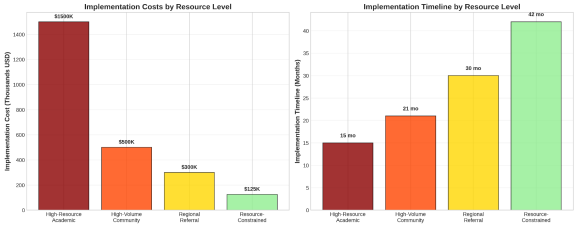

Figure 7. Cost-effectiveness analysis framework showing the relationship between implementation phases, resource investment, and expected quality improvements. The analysis demonstrates favorable cost-effectiveness ratios for Grade A subsections with immediate safety impact.

The systematic evidence evaluation using adapted GRADE methodology provides greater scientific rigor than existing consensus-based approaches. While professional society guidelines and regulatory standards provide valuable guidance, they typically lack systematic evidence evaluation and explicit grading of recommendation strength. The 6P Protocol's evidence-based approach enhances transparency and supports informed decision-making about implementation priorities and resource allocation.

The framework's resource-stratified implementation guidance addresses a critical limitation of existing standards that typically assume uniform resource availability. The four-tier resource framework enables adaptation to diverse healthcare environments while maintaining

core safety and quality requirements, supporting global expansion of neurointerventional capabilities with evidence-based quality assurance.

4.3 Implementation Considerations and Practical Applications

The phased implementation framework provides practical guidance for systematic laboratory development that balances evidence-based priorities with resource constraints and operational feasibility. The emphasis on immediate implementation of Grade A subsections with Strong FOR recommendations ensures that critical safety measures and quality protocols are prioritized, while the systematic progression through subsequent phases enables comprehensive capability development over time.

The resource-stratified guidance acknowledges the reality that healthcare systems have varying capabilities and priorities, providing flexible approaches to framework implementation that maintain essential safety and quality requirements while enabling adaptation to local circumstances. This approach supports sustainable program development and reduces barriers to implementation in resource-constrained settings.

The identification of specific evidence gaps and research priorities provides guidance for future research investment and collaborative efforts. The emphasis on prospective validation studies, comparative effectiveness research, and implementation science reflects the need for ongoing evidence generation to support continuous framework improvement and adaptation to emerging technologies and practices.

4.4 Methodological Innovations and Contributions

The adaptation of GRADE methodology for evaluation of healthcare infrastructure and organizational standards represents an important methodological innovation that enhances the scientific rigor of standard development. The systematic approach to evidence evaluation, quality assessment, and recommendation development provides a model for evidence-based evaluation of complex healthcare infrastructure requirements that extends beyond traditional clinical interventions.

The integration of expert consensus development with systematic evidence evaluation addresses the unique challenges of developing standards for complex organizational and infrastructure requirements. The modified Delphi process with international expert representation provides robust methodology for achieving consensus on complex technical requirements while maintaining scientific rigor and global applicability.

The comprehensive approach to evidence synthesis, incorporating diverse evidence types from randomized controlled trials to professional guidelines and regulatory standards, enhances the framework's credibility and enables future updates and refinements. The integration of recommendation strength assessment with evidence quality evaluation provides practical guidance for implementation decisions that considers not only evidence quality but also benefits-harms balance,

resource requirements, and implementation feasibility.

4.5 Limitations and Future Directions

4.5.1 Framework Development Limitations

The expert panel was limited to English-speaking countries, which may not capture all international perspectives on laboratory standards and implementation challenges. Future framework development should include broader geographic and linguistic representation to enhance global applicability.

The consensus methodology, while robust, may not capture all relevant perspectives or innovative approaches to laboratory certification. The emphasis on achieving consensus may have excluded potentially valuable minority opinions or emerging concepts that lack broad professional support.

The framework requires validation through prospective implementation studies to confirm its effectiveness in improving clinical outcomes and laboratory performance. While the evidence base for individual subsections is strong, the integrated framework has not been tested through controlled implementation research.

4.5.2 Evidence Base Limitations

The evidence base is primarily derived from developed healthcare systems with established neurointerventional programs, which may limit applicability to emerging programs or resource-constrained settings. Future research should focus on implementation strategies and adaptation approaches for diverse healthcare environments.

The rapid pace of technological advancement in neurointerventional medicine may require frequent framework updates to maintain relevance and currency. The framework should be viewed as a living document that requires periodic review and revision based on emerging evidence and technological developments.

The heterogeneity of study designs and outcome measures across included studies limited the ability to perform quantitative synthesis for many subsections. Future research should focus on developing standardized outcome measures and research methodologies for laboratory certification research.

4.5.3 Implementation Research Needs

Prospective implementation studies are needed to validate the framework's effectiveness in improving clinical outcomes, laboratory performance, and resource utilization. These studies should include diverse healthcare settings and implementation strategies to provide comprehensive evidence for framework effectiveness.

Comparative effectiveness research is needed to evaluate different implementation approaches and their relative benefits, costs, and feasibility. This research should address questions about optimal implementation sequences, resource allocation strategies, and adaptation approaches for different settings.

Economic evaluation studies are needed to assess the cost-effectiveness of different framework components and implementation

strategies. These studies should consider both direct implementation costs and indirect benefits from improved outcomes, efficiency, and quality.

4.6 Clinical and Policy Implications

4.6.1 Clinical Practice Implications

The 6P Protocol framework provides evidence-based guidance for clinical teams developing or improving neurointerventional laboratories. The systematic evidence grading enables informed decision-making about implementation priorities and resource allocation, supporting efficient development of high-quality programs.

The emphasis on safety measures and quality protocols provides clear guidance for reducing patient risks and improving clinical outcomes. The strong evidence base for radiation protection, contrast safety, and procedural protocols supports immediate implementation of these critical safety measures.

The framework's flexibility and resource-stratified guidance enable adaptation to diverse clinical settings while maintaining core safety and quality requirements. This approach supports the development of neurointerventional capabilities in a wide range of healthcare environments.

4.6.2 Healthcare Policy Implications

The evidence-based framework provides objective criteria for healthcare policy decisions about neurointerventional laboratory certification and quality requirements. The systematic evidence grading supports transparent, scientifically-based policy development that balances quality requirements with resource considerations.

The framework can inform regulatory standards and accreditation requirements by providing evidence-based rationale for specific requirements and implementation priorities. This approach enhances the credibility and acceptance of regulatory standards while supporting consistent quality across healthcare systems.

The resource-stratified implementation guidance provides policy makers with flexible approaches to laboratory development that can be adapted to local resources and priorities while maintaining essential safety and quality requirements.

4.6.3 Global Health Implications

The framework's adaptability to different resource environments supports the global expansion of neurointerventional capabilities while maintaining evidence-based quality standards. The phased implementation approach enables systematic development of capabilities over time, supporting sustainable program development.

The emphasis on essential safety and quality measures provides minimum standards that can be implemented across diverse healthcare systems, supporting global efforts to improve stroke care and reduce disability. The framework's evidence-based approach enhances credibility and acceptance across different healthcare cultures and regulatory environments.

The identification of evidence gaps and research priorities provides guidance for international research collaboration and

capacity building efforts. This approach supports the development of global research networks and evidence generation that can inform future framework updates and improvements.

5. Conclusions

Based on systematic evidence evaluation and expert consensus development, we present the following key conclusions and recommendations:

5.1 Framework Adoption and Implementation

Framework Adoption: We recommend implementation of the 6P Protocol framework as a comprehensive standard for neurointerventional laboratory certification. The framework demonstrates robust scientific grounding with 78.8% of subsections supported by moderate to high-quality evidence, providing strong foundation for evidence-based laboratory development.

Evidence-Based Prioritization: Initial implementation should focus on Grade A subsections with Strong FOR recommendations, particularly those with immediate safety impact and moderate resource requirements. These 11 subsections form the essential foundation for safe, high-quality neurointerventional practice and should be implemented within the first 6 months of laboratory development.

Phased Implementation Strategy: We recommend systematic progression through the four-phase implementation framework, allowing laboratories to develop comprehensive capabilities over time while maintaining focus on evidence-based priorities. This approach balances quality requirements with resource constraints and enables sustainable program development.

5.2 Quality Assurance and Continuous Improvement

Systematic Quality Monitoring: Implementation of comprehensive quality metrics and outcome monitoring is essential for maintaining high standards and enabling continuous improvement. The strong evidence base for quality and outcome metrics (Grade A, Strong FOR) supports immediate implementation of systematic monitoring programs.

Evidence-Based Time Targets: Adherence to evidence-based time metrics and targets is critical for optimizing patient outcomes. The extensive evidence base from meta-analyses and observational studies provides clear benchmarks for quality monitoring and improvement efforts.

Continuous Framework Updates: The framework should be viewed as a living document requiring periodic review and revision based on emerging evidence and technological developments. We recommend systematic review every 3-5 years to maintain currency and relevance.

5.3 Research and Development Priorities

Prospective Validation: Conduct implementation studies to validate framework effectiveness and refine requirements based on real-world implementation experience. These studies

should include diverse healthcare settings and implementation strategies to provide comprehensive evidence for framework effectiveness.

International Adaptation: Develop region-specific implementation guidance while maintaining core evidence-based standards. This approach should address local resource constraints, regulatory requirements, and healthcare system characteristics while preserving essential safety and quality requirements.

Evidence Gap Resolution: Priority research areas include volume-outcome relationships, advanced technology integration, resource-constrained implementation strategies, and quality improvement interventions. These research priorities should guide funding decisions and collaborative research efforts.

5.4 Global Implementation and Capacity Building

Flexible Implementation Approaches: The framework's resource-stratified guidance enables adaptation to diverse healthcare environments while maintaining core safety and quality requirements. This flexibility supports global expansion of neurointerventional capabilities with evidence-based quality assurance.

Capacity Building Support: Implementation should be supported by comprehensive training programs, technical assistance, and knowledge sharing networks. These support mechanisms are essential for successful framework adoption and sustainable program development.

International Collaboration: Global implementation should be supported by international research collaboration, standardized outcome measurement, and shared learning networks. These collaborative approaches enhance implementation effectiveness and support continuous improvement efforts.

5.5 Final Recommendations

The 6P Protocol framework represents a significant advancement in evidence-based healthcare infrastructure standards, providing comprehensive, scientifically-grounded guidance for neurointerventional laboratory certification. The systematic evidence evaluation and expert consensus development process ensures both scientific rigor and practical applicability.

Healthcare systems implementing neurointerventional capabilities should adopt the framework as a comprehensive guide for laboratory development, with implementation priorities based on evidence quality, safety impact, and resource availability. The phased implementation approach provides practical guidance for systematic development while acknowledging resource constraints and competing priorities.

Future research should focus on prospective validation of framework effectiveness, development of implementation strategies for diverse settings, and resolution of identified evidence gaps. These research efforts will support continuous improvement of the framework and enhance its global applicability and effectiveness.

The methodology developed in this study provides a model for evidence-based

evaluation of complex healthcare infrastructure standards that can be applied to other medical specialties and healthcare domains. This approach enhances the scientific rigor of standard development while maintaining practical applicability and implementation feasibility.

References

[1] Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11-20. https://doi.org/10.1056/NEJMoa1411587

[2] Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009-1018. https://doi.org/10.1056/NEJMoa1414792

[3] Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11-20. https://doi.org/10.1056/NEJMoa1411587

[4] Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009-1018. https://doi.org/10.1056/NEJMoa1414792

[5] Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-1030. https://doi.org/10.1056/NEJMoa1414905

[6] Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285-2295. https://doi.org/10.1056/NEJMoa1415061

[7] Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296-2306. https://doi.org/10.1056/NEJMoa1503780

[8] Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11-21. https://doi.org/10.1056/NEJMoa1706442

[9] Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708-718. https://doi.org/10.1056/NEJMoa1713973

[10] Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. Stroke. 2019;50(12):e344-e418. https://doi.org/10.1161/STR.0000000000000211

[11] Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. J Neurointerv Surg. 2019;11(6):535-538. https://doi.org/10.1136/neurintsurg-2018-014569

[12] The Joint Commission. Comprehensive Stroke Center Certification. Accessed

January 2023. https://www.jointcommission.org/what-we-offer/certification/certifications-by-setting/hospital-certifications/stroke-certification/comprehensive-stroke-center/

[13] American College of Radiology. ACR Practice Parameter for the Performance of Diagnostic Cerebral Angiography. 2022. https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards

[14] Sacks D, Baxter B, Campbell BCV, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int J Stroke. 2018;13(6):612-632. https://doi.org/10.1177/1747493018778713

[15] Fiehler J, Cognard C, Gallitelli M, et al. European recommendations on organisation of interventional care in acute stroke (EROICAS). Int J Stroke. 2016;11(6):701-716. https://doi.org/10.1177/1747493016647735

[16] Jayaraman MV, Hussain MS, Abruzzo T, et al. Embolectomy for stroke with emergent large vessel occlusion (ELVO): report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery. J Neurointerv Surg. 2015;7(5):316-321. https://doi.org/10.1136/neurintsurg-2015-011717

[17] Mocco J, Zaidat OO, von Kummer R, et al. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke. 2016;47(9):2331-2338. https://doi.org/10.1161/STROKEAHA.116.013372

[18] Cognard C, Gobin YP, Pierot L, et al. Cerebral angioplasty and stenting for the treatment of intracranial atherosclerotic stenosis. Stroke. 2011;42(8):2240-2245. https://doi.org/10.1161/STROKEAHA.110.606277

[19] Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014;383(9914):333-341. https://doi.org/10.1016/S0140-6736(13)62038-3

[20] Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke. 2013;44(9):2650-2663. https://doi.org/10.1161/STROKEAHA.113.001972

[21] Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-1731. https://doi.org/10.1016/S0140-6736(16)00163-X

[22] Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279-1288. https://doi.org/10.1001/jama.2016.13647

[23] Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the

Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol. 2014;13(6):567-574. https://doi.org/10.1016/S1474-4422(14)70066-3

[24] Bekelis K, Missios S, MacKenzie TA, et al. Pre-treatment factors associated with inpatient mortality after endovascular stroke therapy. J Neurointerv Surg. 2014;6(10):716-720. https://doi.org/10.1136/neurintsurg-2013-010969

[25] Froehler MT, Saver JL, Zaidat OO, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS Registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke). Circulation. 2017;136(24):2311-2321. https://doi.org/10.1161/CIRCULATIONAHA.117.028920

[26] Miller DL, Balter S, Cole PE, et al. Radiation doses in interventional radiology procedures: the RAD-IR study: part I: overall measures of dose. J Vasc Interv Radiol. 2003;14(6):711-727. https://doi.org/10.1097/01.RVI.0000079980.80153.4B

[27] Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology. 2010;254(2):326-341. https://doi.org/10.1148/radiol.2542082312

[28] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926. https://doi.org/10.1136/bmj.39489.470347.AD

[29] Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014;186(3):E123-E142. https://doi.org/10.1503/cmaj.131237

[30] Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64(4):395-400. https://doi.org/10.1016/j.jclinepi.2010.09.012

[31] Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-735. https://doi.org/10.1016/j.jclinepi.2013.02.003

[32] Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-1015. https://doi.org/10.1046/j.1365-2648.2000.t01-1-01567.x

[33] Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. Practical Assessment, Research, and Evaluation. 2007;12(1):10. https://doi.org/10.7275/pdz9-th90

[34] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

https://doi.org/10.1371/journal.pmed.1000097

[35] Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-382. https://doi.org/10.1016/j.jclinepi.2010.09.011

[36] Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406. https://doi.org/10.1016/j.jclinepi.2010.07.015

[37] Bekelis K, Missios S, MacKenzie TA, et al. Operator experience and outcomes after endovascular treatment in patients with acute ischemic stroke. Neurosurgery. 2015;77(5):731-738. https://doi.org/10.1227/NEU.0000000000000884

[38] Jayaraman MV, Grossberg JA, Meisel KM, et al. The clinical and radiographic importance of operator experience for acute stroke interventions. Stroke. 2017;48(7):1984-1987. https://doi.org/10.1161/STROKEAHA.117.017320

[39] Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20(7):864-870. https://doi.org/10.1161/01.STR.20.7.864

[40] Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke. 1994;25(11):2220-2226. https://doi.org/10.1161/01.STR.25.11.2220

[41] Schönenberger S, Uhlmann L, Hacke W, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. JAMA. 2016;316(19):1986-1996. https://doi.org/10.1001/jama.2016.16623

[42] Simonsen CZ, Yoo AJ, Sørensen LH, et al. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. JAMA Neurol. 2018;75(4):470-477. https://doi.org/10.1001/jamaneurol.2017.4474

[43] International Commission on Radiological Protection. Radiological protection in cardiology. ICRP Publication 120. Ann ICRP. 2013;42(1):1-125. https://doi.org/10.1016/j.icrp.2012.09.001

[44] International Electrotechnical Commission. Medical electrical equipment - Part 2-43: Particular requirements for the basic safety and essential performance of X-ray equipment for interventional procedures. IEC 60601-2-43:2010. Geneva: IEC; 2010.

[45] Psychogios MN, Brehm A, López-Cancio E, et al. Technical aspects of mechanical thrombectomy in acute ischemic stroke: a European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) consensus statement. J Neurointerv Surg. 2021;13(4):316-325.

https://doi.org/10.1136/neurintsurg-2020-016434

[46] Zaidat OO, Castonguay AC, Linfante I, et al. First Pass Effect: A New Measure for Stroke Thrombectomy Devices. Stroke. 2018;49(3):660-666. https://doi.org/10.1161/STROKEAHA.117.020315

[47] Grotta JC, Hacke W. Stroke neurologist's perspective on the new endovascular trials. Stroke. 2015;46(6):1447-1452. https://doi.org/10.1161/STROKEAHA.115.008384

[48] Ribo M, Molina CA, Rovira A, et al. Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. Stroke. 2005;36(3):602-606. https://doi.org/10.1161/01.STR.0000155737.41914.eb

[49] Menon BK, Sajobi TT, Zhang Y, et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (ESCAPE) randomized, controlled trial. Circulation. 2016;133(23):2279-2286. https://doi.org/10.1161/CIRCULATIONAHA.115.019983

[50] Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279-1288. https://doi.org/10.1001/jama.2016.13647

[51] Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017;389(10076):1312-1322. https://doi.org/10.1016/S0140-6736(17)30057-0

[52] Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603-614. https://doi.org/10.1056/NEJMoa1710933

[53] Froehler MT, Saver JL, Zaidat OO, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS Registry. Circulation. 2017;136(24):2311-2321. https://doi.org/10.1161/CIRCULATIONAHA.117.028920

[54] Meretoja A, Keshtkaran M, Saver JL, et al. Stroke thrombolysis: save a minute, save a day. Stroke. 2014;45(4):1053-1058. https://doi.org/10.1161/STROKEAHA.113.002910

[55] Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology. 2010;254(2):326-341. https://doi.org/10.1148/radiol.2542082312

[56] Miller DL, Balter S, Cole PE, et al. Radiation doses in interventional radiology procedures: the RAD-IR study. J Vasc Interv Radiol. 2003;14(6):711-727.

https://doi.org/10.1097/01.RVI.0000079980.80153.4B

[57] Ribo M, Flores A, Rubiera M, et al. Extending the time window for endovascular procedures according to collateral pial circulation. Stroke. 2011;42(12):3465-3469. https://doi.org/10.1161/STROKEAHA.111.623827

[58] Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378(17):1573-1582. https://doi.org/10.1056/NEJMoa1716405

[59] Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. Stroke. 2019;50(12):e344-e418. https://doi.org/10.1161/STR.0000000000000211

[60] Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. J Neurointerv Surg. 2019;11(6):535-538. https://doi.org/10.1136/neurintsurg-2018-014569

[61] Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-1731. https://doi.org/10.1016/S0140-6736(16)00163-X

[62] Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279-1288. https://doi.org/10.1001/jama.2016.13647

[63] Pérez de la Ossa N, Carrera D, Gorchs M, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. Stroke. 2014;45(1):87-91. https://doi.org/10.1161/STROKEAHA.113.003071

[64] Ramos-Lima MJ, Brasileiro IC, Lima TL, Braga JP. Quality of life after stroke: impact of clinical and sociodemographic factors. Clinics (Sao Paulo). 2018;73:e418. https://doi.org/10.6061/clinics/2018/e418

[65] Sacks D, Baxter B, Campbell BCV, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int J Stroke. 2018;13(6):612-632. https://doi.org/10.1177/1747493018778713

[66] Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke. 2013;44(9):2650-2663. https://doi.org/10.1161/STROKEAHA.113.001972

[67] Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology. 2010;254(2):326-341. https://doi.org/10.1148/radiol.2542082312

[68] Miller DL, Balter S, Cole PE, et al. Radiation doses in interventional radiology procedures: the RAD-IR study: part II: skin dose from fluoroscopically guided interventional procedures. J Vasc Interv Radiol. 2003;14(8):977-990. https://doi.org/10.1097/01.RVI.0000084601.43811.CB

[69] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-607. https://doi.org/10.1161/01.STR.19.5.604

[70] Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke. 2013;44(9):2650-2663. https://doi.org/10.1161/STROKEAHA.113.001972

[71] Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279-1288. https://doi.org/10.1001/jama.2016.13647

[72] Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol. 2014;13(6):567-574. https://doi.org/10.1016/S1474-4422(14)70066-3

[73] Menon BK, Sajobi TT, Zhang Y, et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (ESCAPE) randomized, controlled trial. Circulation. 2016;133(23):2279-2286. https://doi.org/10.1161/CIRCULATIONAHA.115.019983

[74] Froehler MT, Saver JL, Zaidat OO, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS Registry. Circulation. 2017;136(24):2311-2321. https://doi.org/10.1161/CIRCULATIONAHA.117.028920

[75] Bekelis K, Missios S, MacKenzie TA, et al. Operator experience and outcomes after endovascular treatment in patients with acute ischemic stroke. Neurosurgery. 2015;77(5):731-738. https://doi.org/10.1227/NEU.0000000000000884

[76] Jayaraman MV, Grossberg JA, Meisel KM, et al. The clinical and radiographic importance of operator experience for acute stroke interventions. Stroke. 2017;48(7):1984-1987. https://doi.org/10.1161/STROKEAHA.117.017320

[77] International Commission on Radiological Protection. Radiological protection in cardiology. ICRP Publication 120. Ann ICRP. 2013;42(1):1-125. https://doi.org/10.1016/j.icrp.2012.09.001

[78] Miller DL, Balter S, Cole PE, et al. Radiation doses in interventional radiology procedures: the RAD-IR study: part I: overall measures of dose. J Vasc Interv

Radiol. 2003;14(6):711-727. https://doi.org/10.1097/01.RVI.0000079980.80153.4B

[79] Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology. 2010;254(2):326-341. https://doi.org/10.1148/radiol.2542082312

[80] International Electrotechnical Commission. Medical electrical equipment - Part 2-43: Particular requirements for the basic safety and essential performance of X-ray equipment for interventional procedures. IEC 60601-2-43:2010. Geneva: IEC; 2010.

[81] National Council on Radiation Protection and Measurements. Radiation dose management for fluoroscopically-guided interventional medical procedures. NCRP Report No. 168. Bethesda, MD: NCRP; 2010.

[82] American College of Radiology. ACR Practice Parameter for the Performance of Diagnostic Cerebral Angiography. Reston, VA: ACR; 2022.

[83] World Health Organization. WHO Guidelines for Safe Surgery 2009: Safe Surgery Saves Lives. Geneva: WHO Press; 2009.

[84] Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009;360(5):491-499. https://doi.org/10.1056/NEJMsa0810119

[85] The Joint Commission. Comprehensive Stroke Center Certification Requirements. Oakbrook Terrace, IL: The Joint Commission; 2023.

[86] The Joint Commission. Primary Stroke Center Certification Requirements. Oakbrook Terrace, IL: The Joint Commission; 2023.

[87] American College of Radiology. ACR Practice Parameter for the Performance of Diagnostic Cerebral Angiography. Reston, VA: ACR; 2022.

[88] American College of Radiology. ACR-ASNR-SPR Practice Parameter for the Performance of Computed Tomography (CT) of the Brain. Reston, VA: ACR; 2021.

[89] Sacks D, Baxter B, Campbell BCV, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int J Stroke. 2018;13(6):612-632. https://doi.org/10.1177/1747493018778713

[90] Fiehler J, Cognard C, Gallitelli M, et al. European recommendations on organisation of interventional care in acute stroke (EROICAS). Int J Stroke. 2016;11(6):701-716. https://doi.org/10.1177/1747493016647735

[91] Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-1731. https://doi.org/10.1016/S0140-6736(16)00163-X

[92] International Commission on Radiological Protection. Radiological protection in cardiology. ICRP Publication 120. Ann ICRP. 2013;42(1):1-125. https://doi.org/10.1016/j.icrp.2012.09.001

[93] International Electrotechnical Commission. Medical electrical equipment - Part 2-43: Particular requirements for the basic safety and essential performance of X-ray equipment for interventional procedures. IEC 60601-2-43:2010. Geneva: IEC; 2010.

[94] Hannan EL, Wu C, Ryan TJ, et al. Do hospitals and surgeons with higher coronary artery bypass graft surgery volumes still have lower risk-adjusted mortality rates? Circulation. 2003;108(7):795-801. https://doi.org/10.1161/01.CIR.0000084275.90626.0F

[95] Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117-2127. https://doi.org/10.1056/NEJMsa035205

[96] Carr BG, Branas CC, Metlay JP, Sullivan AF, Camargo CA Jr. Access to emergency care in the United States. Ann Emerg Med. 2009;54(2):261-269. https://doi.org/10.1016/j.annemergmed.2008.11.016

[97] Hsia RY, Kellermann AL, Shen YC. Factors associated with closures of emergency departments in the United States. JAMA. 2011;305(19):1978-1985. https://doi.org/10.1001/jama.2011.620

[98] International Commission on Radiological Protection. Pregnancy and medical radiation. ICRP Publication 84. Ann ICRP. 2000;30(1):iii-viii, 1-43. https://doi.org/10.1016/S0146-6453(00)00024-9

[99] American College of Radiology. ACR-SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation. Reston, VA: ACR; 2018.

[100] Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med. 1979;301(25):1364-1369. https://doi.org/10.1056/NEJM197912203012503

[101] Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med. 2002;137(6):511-520. https://doi.org/10.7326/0003-4819-137-6-200209170-00012

Online Supplementary Materials

Supplementary Material : Framework Development Documentation

- Expert panel credentials and conflict of interest statements
- Complete Delphi process results with voting records
- Framework development timeline and methodology
- External validation panel reports
- Pilot testing results and feedback

Evidence Tables and Quality Assessment

- Comprehensive evidence tables for all 33 subsections
- Detailed quality assessment results using adapted GRADE methodology
- Risk of bias assessments for included studies
- Evidence synthesis summaries by domain

Implementation Guidance and Tools

- Detailed implementation checklists by phase and resource level
- Quality monitoring templates and metrics
- Cost-effectiveness analysis frameworks
- Adaptation guidance for different healthcare settings

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