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## A primer for clinical researchers in the emergency department: Part 9.

### How to conduct a systematic review in the field of Emergency Medicine.

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All authors contributed to the concept of this paper, drafting and revising the manuscript; and agree to be accountable for the accuracy and integrity of the work.

### **Running Title**

Systematic reviews in emergency medicine.

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**Abstract**

In this series we address important topics for emergency clinicians who either participate in research as part of their work, or use the knowledge generated by research studies. Emergency clinicians are routinely in the position of applying new evidence in clinical practice. With an ever-increasing volume of evidence generated, this can be problematic when studies are conducted in different settings, and include different patient groups, different interventions, and different outcomes. This is made even more difficult when the results of primary research studies do not agree. Systematic reviews are becoming increasingly valuable as they appraise and synthesise research findings using a clear methodology, and summarise the results of primary studies. As such, systematic reviews help translate research findings into clinical practice. This paper provides a practical starting point for understanding the steps involved in conducting a systematic review in emergency medicine and will help readers appraise the findings of systematic reviews.

**Keywords:** emergency medicine, research, methodology, systematic review, meta-analysis.

*“It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, updated periodically, of all relevant randomised controlled trials.”*

- Archie Cochrane, 1979

## **Introduction**

A series of primers for clinical researchers in Emergency Medicine has been published in this journal.<sup>1,2</sup> This paper discusses the purpose, design, and conduct of systematic reviews in Emergency Medicine.

Systematic reviews are becoming increasingly important for clinicians to summarise the results of primary research studies and if possible, provide pooled estimates of the effects of specific interventions. They are different from literature reviews, as they pre-specify all methods prior to the conduct of the full review, ideally as a registered or published protocol. A systematic search of the literature is conducted, aiming to identify, retrieve, assess and summarise all relevant studies on the topic of interest in a reproducible manner. Important elements include a critical appraisal of the primary research studies included in the review (assessment of the risk of bias

and study quality), and an assessment of the certainty of the body of evidence as a whole (assessment of the strength of the evidence).

The aim of this article is to provide guidance for emergency clinicians undertaking systematic reviews, highlighting resources that may be of help at different stages of the process. It will also assist readers of systematic reviews to understand their key components, how they are organised, how critical appraisal is performed, and how certainty of evidence is evaluated.

### **What is a systematic review?**

The Cochrane Collaboration defines a systematic review as “a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant primary research, and to collect and analyse data from the studies that are included in the review”.<sup>3</sup> Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included research.

A systematic review aims to synthesise all evidence that fits pre-specified eligibility criteria to answer a clearly formulated question. Systematic reviews adhere to standardised methodology for identifying, critically evaluating, and reporting findings with a view to minimising bias and providing more reliable findings to inform evidence-based decision making regarding individual patients, health policy, or to inform clinical practice guidelines. They may be undertaken to evaluate disease diagnosis, prevalence, aetiology, prognosis, or treatment.

Key components of systematic reviews include: a clearly stated set of objectives with pre-defined eligibility criteria for included studies, explicit reproducible methods including a systematic attempt to identify all studies that meet eligibility criteria, an assessment of the methodological quality of the included primary studies, and systematic synthesis and presentation of findings.<sup>4</sup>

### **Why conduct a systematic review?**

Research in emergency medicine and critical care is increasing in volume, making it difficult for clinicians to keep up-to-date with research evidence. Though the volume of research is ever increasing, studies in acute care can be difficult to conduct, may include small numbers of patients, and may not be generalisable outside of the setting in which they were conducted. As such, translating this evidence into clinical practice and healthcare policy can be challenging. Systematic reviews can provide a summary of the most up-to-date research evidence, and may include an assessment of the strengths and limitations of available evidence. Systematic reviews in emergency medicine are increasing in number, as evidenced by the recent creation of the Cochrane Acute and Emergency Care Group.<sup>5</sup>

Systematic reviews group similar primary research studies together and explore clinical and statistical heterogeneity across studies. In emergency medicine, primary research studies may

vary in terms of setting, population (P), the intervention (I), comparisons (C), and the outcomes (O) of interest (the PICO elements). By examining the PICO elements, systematic reviews can make a judgment about the extent of variability across the included primary studies, and if the studies are sufficiently similar to meta-analyse.

In clinical specialties like emergency medicine, the summary of existing evidence derived from systematic reviews may be incorporated into clinical practice guidelines or health policies, which may improve dissemination and translation of primary research studies.

### **Guidance for conducting systematic reviews**

Several organisations have developed guidance documents or instruction manuals for the authors of systematic reviews, such as the Cochrane Collaboration, the Joanna Briggs Institute, EPPI-Centre and the Centre for Reviews and Dissemination.

*The Cochrane Collaboration* produces high quality systematic reviews and publishes them in the Cochrane Library, ‘a leading resource database for systematic reviews in health care’.<sup>7</sup> Cochrane reviews are prepared by volunteer authors who register with one of 52 Cochrane Review Groups. The Cochrane Review Groups have specific themes and are led by a co-ordinating editor and editorial team. Each group provides authors with methodological and editorial support, including peer review, for the type of systematic review being conducted. The Cochrane Editorial

Committee coordinates the writing of the guidance documents for the design and conduct of systematic reviews, including: Cochrane Handbook for Systematic Reviews of Interventions,<sup>4</sup> and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.<sup>8</sup> Cochrane provides training for systematic review authors through their training site, webinars, and an annual conference.

The *Centre for Reviews and Dissemination* specialises in ‘evidence synthesis, assembling and analysing data from multiple primary research studies to generate policy relevant to research’.<sup>9</sup> The Centre for Reviews and Dissemination database houses systematic reviews conducted by their group and by others. In line with other organisations, they have produced guidance on undertaking systematic reviews and hold regular training courses.

The *Joanna Briggs Institute* is the ‘international, not-for-profit, research and development centre within the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia’.<sup>10</sup> The Joanna Briggs Institute produces systematic reviews based on previously identified topics or on topics suggested by authors. Free access to some systematic reviews is provided through the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports. The Joanna Briggs institute also provides systematic review training and write guidance documents.<sup>11</sup>

The *EPPI-Centre* is involved in ‘developing methods for systematic reviews and research synthesis, conducting reviews, supporting others to undertake reviews, and providing training and guidance in this area’.<sup>12</sup> The Index to the Knowledge Library provides users with the ability to search for key messages within specific subject areas to which EPPI-Centre reviews have contributed. The EPPI-Centre has published *An Introduction to Systematic Reviews* and provides online learning resources to help guide authors.<sup>13</sup>

### **Reporting standards for systematic reviews of different types**

Reporting standards specify a minimum information set needed for a complete account of what was done during a systematic review. Reporting standards are intended to be used prior to submission of systematic reviews for publication, often in checklist form. The Enhancing the QUALity and Transparency Of health Research (EQUATOR) Network is a global initiative that aims to enhance the quality and transparency of health research.<sup>14</sup> The EQUATOR Network assists in the development, dissemination and implementation of reporting guidelines, and is also a database of reporting guidelines for different systematic review types (Table 1 provides reporting standards for systematic reviews of interventional studies, studies of diagnostic test accuracy, and observational studies).

**Table 1.** Reporting standards for different types of reviews

Type of study	Recommended reporting guideline
Protocols for Systematic reviews with or without meta-analyses	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)
Systematic reviews with or without meta-analyses	Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement <sup>15</sup>
Systematic reviews of diagnostic test accuracy	Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement <sup>16</sup>
Systematic reviews with meta-analyses of observational data	Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology group <sup>17</sup>

### **Planning the conduct of a systematic review**

The first step in planning the conduct of a systematic review is to develop a clearly formulated question. Systematic review questions may relate to treatment or therapy, medical devices, disease prevention, diagnosis, prognosis or risk stratification, disease causation, or patient / carer

/ health-care provider experiences. Ideally, the research question should be clearly formulated and of relevance to clinical practice, and the review authors should have an interest in the topic under review. Review questions investigating therapeutic interventions or outcomes should be formatted using the PICO elements,<sup>6</sup> while qualitative studies may be formulated in the Population, Exposure, Outcomes (PEO) format.<sup>18</sup>

The second step in planning the conduct of a systematic review is to determine if a systematic review is needed. This involves (a) searching for an existing review that addresses the research question, and (b) ensuring that a review similar to the one planned has not already been undertaken. A search of the Cochrane Database of Systematic Reviews,<sup>19</sup> the PROSPERO database (an international prospective register of systematic reviews),<sup>20</sup> and some other repositories and sites,<sup>21,22</sup> will identify existing or planned systematic reviews.

The third step in planning the conduct of a systematic review is to determine the feasibility of undertaking the review. This includes identifying key people to help design and conduct the systematic review, ensuring a balance of clinical and methodological expertise, and ensuring that sufficient time is available to conduct the systematic review within its anticipated scope.

### **Developing a systematic review protocol**

Once the systematic review question has been developed, and it has been determined that a systematic review is needed and feasible, the systematic review protocol can be developed. A systematic review protocol is the planned and documented methodology used to conduct the review. The protocol prevents arbitrary decision making with respect to inclusion criteria and extraction of data, thus reducing the likelihood of selective reporting of positive outcomes. A systematic review protocol describes in advance the rationale for the review question, the proposed methods for retrieving and selecting primary research studies, for assessing the risk of bias and certainty of the evidence, and for analysing and presenting the results. The protocol should include sufficient detail so that the systematic review could be independently reproduced. Checklists have been developed to improve the reporting of systematic review protocols.<sup>23</sup> Systematic review protocols can be registered online through PROSPERO or other databases, repositories, or published as stand-alone articles.<sup>24</sup> The components of a systematic review protocol are outlined in Figure 1.

*Purpose:*

The purpose outlines the importance and rationale for undertaking the systematic review. This should provide clear direction, describe previous systematic reviews in the area and their strengths and limitations, and clarify how the proposed review will fill gaps in the literature or provide new information that could improve practice. Should previous systematic reviews be identified, they should be examined for current relevance (have new studies on the same topic

been published?), risk of bias/quality (were appropriate methods used?), and similarity (was the same population / intervention / outcome evaluated?). The AMSTAR 2 tool or the ROBIS tool may be helpful in assessing the quality of previously performed systematic reviews.<sup>25</sup>

*Objectives:*

The objective (s) of the systematic review should relate directly to the research question, and should be designed using the PICO or PEO elements used in formulating the research question.

*Scope:*

Pre-defining the eligibility criteria for inclusion of studies in the systematic review using the following domains determines the scope of the systematic review.

Type of studies. The research question will determine the study design for inclusion; questions regarding therapies or interventions may involve searching pilot studies, randomized controlled trials, non-randomised studies, cohort studies, cross-sectional studies or case-controlled studies. Questions regarding prognosis or risk stratification may best be answered using cohort studies. Questions regarding experiences or perceptions may best be answered using qualitative studies.

Participants. The specific patient population, diagnosis, setting, and severity / duration of disease are important to define and will highlight variation among included studies.

Intervention. A detailed description of the interventions that will be included and excluded should be provided. Definition of included treatments, interventions, and management strategies should be described.

Comparison or control intervention. The inclusion and exclusion criteria for all of the comparative or control groups should be pre-specified.

Outcome measures. The primary and secondary outcomes (objective and subjective) that will be included and excluded, and how they will be measured, should be pre-specified and defined in detail. A primary outcome should always include a safety outcome (e.g. adverse event). Pre-specifying the primary and secondary outcomes reduces the likelihood of Type I error (i.e., finding a statistically significant treatment effect just by chance, in the absence of a true treatment effect) and outcome reporting bias (i.e., selectively reporting outcomes based on the strength and/or direction of the findings). Pre-specified outcomes include information about five elements:

- domain (e.g. quality of life)

- specific measurement/type of scale (e.g. rating scale used - it is good practice to choose validated scales; create a hierarchy of which scales you will choose if more than one is reported in the trial)
- specific metric (e.g. change from baseline)
- method of aggregation (e.g. mean)
- time-points/ timing of measurement (e.g. 3 months, 6 months; again use a decision hierarchy).<sup>26</sup>

The choice of outcomes should not be influenced by the findings of the trials, and should be chosen based on perceived clinical importance and/or importance to patients.

*Search methods:*

The aim of the search strategy is to generate a comprehensive list of primary research studies which are relevant to the research question.

The search strategy may involve breaking down the research question into keywords for use in database searching, and by using Medical Subject Headings (MeSH).<sup>27</sup> Keywords may be combined using Boolean Operators (AND, OR, NOT). Search strategies in other similar reviews may be used.

A comprehensive review should search three or more bibliographical databases, clinical trial registries, and unpublished “grey” literature. The Cochrane Database of Systematic Reviews,<sup>19</sup> MEDLINE, Excerpta Medica database (Embase), and PubMed<sup>28</sup> are electronic databases of journal citations and abstracts for biomedical literature. PubMed is a free database, while access to MEDLINE and Embase requires a subscription. Embase and MEDLINE should both be included in the search strategy, as only 34% of journals overlap between the two.<sup>29</sup> Other databases, such as the Cumulative Index to Nursing and Allied Health Literature<sup>30, 30</sup> PsycINFO,<sup>31</sup> and Allied and Complementary Medicine<sup>32</sup> may also be included depending on the clinical topic. A comprehensive list of databases is published through The Centre for Reviews and Dissemination.<sup>9</sup> Clinical trial registries may be searched for studies that have been conducted but not yet published. These include the Australian and New Zealand Clinical Trials Registry, the International Clinical Trials Registry Platform, and ClinicalTrials.<sup>33</sup> In addition, hand searching reference lists of key articles, direct contact with authors, and a search of ‘grey literature’ (unpublished conference proceedings, abstracts, and PhD theses), and books may be included. Databases for searching the grey literature include major online search engines, and specialised databases such as the National Technical Information Service in the United States<sup>34</sup> and the Health Management Information Consortium in the United Kingdom.<sup>35</sup> Conference proceedings are contained in databases such as BIOSIS Previews, the Index to Scientific and Technical Proceedings (ISTP), Zetoc, and the Conference Papers Index.<sup>36-38</sup> At the final stage of the literature search, some limits may be applied. These may restrict the search to the English

language, to human studies, or to a specified date range. The rationale for any search limits should be described.

*Assessing the quality of included studies:*

The methodology that will be used to determine the quality of included studies using the following domains should be pre-specified, and should include a statement regarding how studies of poor methodological quality will be used.

Assessment of the methodological quality (risk of bias) of studies.

The aim of an appraisal of the risk of bias of the primary studies is to determine whether the study is free from methodological bias. The risk of bias/quality of the primary studies that make up the systematic review determines the strength of the conclusions it generates. Validated tools for assessing the risk of bias and quality of included studies have been developed for specific types of primary studies. The QUADAS-2 checklists, the Cochrane RoB 2 for randomised controlled trials, and ROBINS-I tool for observational studies have been validated.<sup>39-42</sup> Numeric scoring systems for risk of bias and quality should be avoided,<sup>43-45</sup> as calculating a summary score involves assigning ‘weights’ to different items in the scale, where the weights assigned are ordinal (represent order but not value). Furthermore, summary scores have been shown to be unreliable assessments of validity.<sup>46</sup> The Cochrane Handbook states: “The use of scales

[summary scores] for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews”.<sup>4</sup>

Biases typically assessed for an RCT are selection bias (was there proper random sequence generation? was there proper concealment of allocation?), performance bias (was there blinding of participants and personnel?), detection bias (was there blinding of outcome assessment?), attrition bias (were data complete?) and outcome reporting bias (was there complete reporting of all outcome data?).

The methodological quality (risk of bias assessment) of studies (i.e., how well the study is conducted) is often confused with quality of reporting (i.e., reporting of all methods used and results). Methodological quality refers to the identification of systematic flaws bias or limitations in the design, conduct, or analysis of research that may distort the study findings.<sup>47</sup> Reporting quality refers to the description of the methods and findings.<sup>48</sup> Both the methodological quality and the quality of reporting should be assessed and included in a systematic review.

Assessment of reporting or publication bias. Publication bias is a type of bias inherent to systematic reviews, where studies with positive results are more likely to be published compared to studies with null results. Comprehensive searches help to minimise publication bias. Funnel plots can be used to visually assess for publication bias provided there are sufficient number of

included studies for each outcome (i.e. ten or more primary studies per outcome).<sup>4</sup> Statistical tests for publication bias include the Egger, Begg, or Peter's tests for funnel plot asymmetry.<sup>49</sup>

Assessment of the certainty or quality of the evidence. Assessment of the certainty of a body of evidence should be undertaken using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>50</sup> The GRADE working group defines certainty of a body of evidence (sometimes referred to as the quality/strength of the evidence) as “the extent of our confidence that the estimates of the effect are correct or are adequate to support a particular decision or recommendation”. Review authors evaluate the body of evidence for a given question and outcomes based on key domains: risk of bias, consistency of effects, imprecision, indirectness, publication bias. In general, evidence from RCTs start at high quality and evidence from observational studies start at low quality, which can be upgraded or downgraded by the review authors. The final rating of the certainty of the evidence is divided into one of four categories: high, moderate, low, or very low.

#### *Reporting:*

Systematic reviews of quantitative data may include statistical pooling (meta-analysis), while qualitative data may be synthesised using different methods.<sup>51</sup> Table 2 outlines guidance documents for reporting the results of quantitative and qualitative data. Where population, intervention and outcome of the primary studies are clinically, methodologically and statistically similar then meta-analysis can be done by pooling appropriate data. The comparisons that will be

included in meta-analysis, the types of data that will be included and outcomes, the statistical methods for pooling, and the effect measure to be used should be pre-specified. Where heterogeneity between studies exists, options include: not performing a meta-analysis (descriptive summary of the data), performing meta-analysis incorporating heterogeneity using a random-effects model, performing subgroup analysis (ideally pre-specified in the study protocol), or excluding outlying studies with a pre-specified rationale (sensitivity analysis).<sup>4</sup>

**Table 2: Guidance on how to conduct meta-analyses for different systematic review types**

Type of systematic review	Name of guidance document
Systematic reviews with or without meta-analyses of health care interventions	Cochrane Handbook of Systematic Reviews of Interventions <ul style="list-style-type: none"> <li>- Chapter 10: Analysing data and undertaking meta-analyses; -</li> <li>- Chapter 6: Choosing effect measures and computing estimates of effect</li> <li>- Chapter 15: Interpreting results and drawing conclusions</li> </ul>
Systematic reviews of Diagnostic Test Accuracy	Handbook for DTA Reviews from the Cochrane Screening and Diagnostic Tests Methods Group
Systematic reviews of	Chapter 13: Including non-randomised studies from the

observational data	Cochrane Handbook of Systematic Reviews of Interventions Joanna Briggs Institute guidance documents
Equity-focused systematic reviews	Guidance from the Campbell and Cochrane Equity Methods Group

### **Conducting the systematic review**

Once the systematic review protocol has been finalised and registered or published, the systematic review may be conducted. The initial step is to perform a literature search according to the search strategy outlined above. The date of the literature search should be logged. Two independent review authors should manually screen the title and abstracts of identified articles. Articles passing title and abstract screening should be reviewed in full text by two independent review authors to reduce error in missing relevant studies for inclusion. Discussion of any discrepancies in study selection should be coordinated between the two review authors. A flowchart may be used to report the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>23</sup> Some software packages, such as Covidence, allow multiple review authors to conduct screening and data extraction, record reasons for article exclusion, and produce PRISMA flowcharts.<sup>52</sup> A table of excluded studies should be added as a supplementary file.

*Data extraction:*

Data extraction involves going back to the primary article, highlighting relevant information, and extracting the data. Two review authors should independently extract data to reduce data extraction errors. Disagreements should be resolved through consensus or third party review author if necessary. Data should be extracted to a standardized paper or electronic form. These forms may be piloted between review authors to calibrate extraction. The type of data extracted will depend on the type of systematic review being performed, but will typically include the type of study, the number of participants, the PICO elements, summary statistics and effect size. Included studies, their characteristics, and data extracted should be tabulated.<sup>51</sup>

*Assessment of the quality of included studies:*

Two review authors should assess the risk of bias and quality of studies and resolve disagreement through a consensus process. The quality of included studies should be assessed and reported according to the study protocol as outlined above.

*Summary of systematic review findings and synthesis:*

A first step in summarising the results of primary studies is to order results by intervention, populations, outcomes, risk of bias, certainty of the evidence and other characteristics. Results should be summarised in tables and figures as well as descriptively. A non-statistical summary of the evidence should address the following points: are the data, design, and characteristics of

included studies similar or different? Are there important trends or themes? Do the data seem to point in one direction? Are there limitations of the systematic review that need to be acknowledged? For systematic reviews including meta-analysis, if the results between studies are similar, they can be combined statistically using meta-analysis. For qualitative or mixed-method reviews, other methods of summarising the evidence may be used.<sup>53</sup> An example of a Cochrane summary table of bias judgements by review authors is shown in Figure 2 (reproduced, with permission, from John Wiley & Sons, Inc).

#### *Deviations to the protocol*

A section called 'deviations to the protocol' should be added which outlines the post hoc rationale and decisions made to the review (e.g. new subgroup analyses). This section is important as the systematic review should be replicable by any outside groups, and should be transparent in the methods used and changed.

#### *Interpretation of the results and drawing conclusions:*

The discussion section should begin with a summary of the major findings of the systematic review taking into account the assessment of the certainty of the evidence. The relevance of the systematic review's research question should be considered and compared to the objectives of the included studies. Results should not emphasise statistical significance of one outcome, but should present a balanced assessment of all outcomes if multiple analyses are reported in a

systematic review. Confidence intervals should be reported as they provide information about the precision of an estimate as well as whether it crosses the null value. The clinical significance of the results should be evaluated and presented.

This section should also include the review findings in relation to the study background, compares the findings to similar reviews on the topic, the theoretical framework, the strengths and limitations of the systematic review, and recommendations for practice and future research.

*Reporting:*

The PRISMA format should be used to report findings of systematic reviews.<sup>54</sup> The PRISMA checklist may be used to check if the methods, results, and discussion sections of the published systematic review have been adequately reported. Endorsement of PRISMA when submitting a paper for publication is required by many journals.

*Conclusions:*

Many organisations provide guidance and detailed instructions on how to conduct a reliable and valid systematic review. Conducting a high quality systematic review takes considerable time, resources, and skill by the review team. However, by following rigorous methodology, the results can provide the best evidence to guide clinical practice, develop clinical practice guidelines, and inform healthcare policy.

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**Competing interests.**

FEB is an Emergency Medicine Australasia section editor for Paediatric Emergency Medicine

ET is an editor for the Cochrane Effective Practice and Organisation of Care Group.

CL is an editor for the Cochrane Hypertension Group.

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Craven 2001	+	+	+	+	+	+	+
Goggin 2001	+	+	+	+	+	+	+
Lew 1990	?	?	+	+	+	+	+
Mirkinson 2000	?	?	+	+	?	?	?
Ozdemir 2003	?	?	?	?	?	?	?
Rayner 1987	?	?	+	+	+	?	+
Storr 1986	?	?	+	+	+	?	+

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