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REVIEW ARTICLE

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Creation of an inventory of quality markers used to evaluate pharmacokinetic literature: A systematic review

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Abstract

What is known and objective: Robust critical appraisal tools for clinical pharmacokinetic studies are limited. Before development of such a tool is possible, quality markers (items deemed important for credibility of study results) must be identified. We aim to create an inventory of quality markers intended for the appraisal of clinical pharmacokinetic studies and to categorize identified markers into associated domains of study quality.

Methods: Medline via ProQuest central (1946–Sep 2020, EMBASE (1974–Sep 2020), Cochrane database of systematic reviews, Google and Google Scholar were searched using the following search categories: pharmacokinetics, reporting guidelines and quality markers. Reference lists of the identified articles were searched manually. Any article (review, study or guideline) reporting quality markers related to the appraisal of pharmacokinetic literature was eligible for inclusion. Articles were further screened and limited to those reported in English on human subjects only. Cell-based and animal-based pharmacokinetic studies were excluded. Extracted data from included articles included identified or perceived markers of quality and baseline article data. Identified quality markers were then categorized according to manuscript reporting domains (abstract, introduction/background, methodology, results, discussion and conclusion).

Results and discussion: Of 789 studies identified, 17 articles were included for extraction of quality markers. A total of 35 quality markers were identified across eight categories. The most frequently reported quality markers were related to method (13/35) and result sections (6/35). Quality markers encompassed all aspects of study design and reporting and were both similar and different to established reporting checklists for clinical pharmacokinetic studies.

What is new and conclusion: The inventory of quality markers is now suitable to undergo further testing for inclusion in a tool designed for the appraisal of clinical pharmacokinetic studies.

KEYWORDS
clinical pharmacokinetics, critical appraisal, pharmacokinetics, quality markers, reporting checklist

1 | WHAT IS KNOWN AND OBJECTIVE

Clinical pharmacokinetic studies are rapidly advancing our knowledge pertaining to how patients and populations respond variably to drugs. Data from clinical pharmacokinetic studies are commonly used to make decisions for drug approvals and funding, and also support clinical decision-making in patient care settings.[1] In particular, these studies provide guidance on difficult-to-treat and dose case scenarios, such as those patients with organ dysfunction, obesity, comorbid conditions or those taking other drugs prone to drug-drug interactions.[2] In the era of individualized medicine, clinical pharmacokinetic studies are becoming very important for understanding drug response characteristics that may influence efficacy and/or safety for patients with profiles or characteristics outside of large phase III studies.[3,4] Due to the high utility of these studies for both drug approval/funding and clinical decision-making, it is essential that published studies are of high quality and that results are interpreted in light of actual and potential sources of bias.[5] As such, these studies should be prone to rigorous appraisals, based on quality markers specific for pharmacokinetic studies. Critical appraisal of scientific literature is a foundation for the evidence-based healthcare movement and important for ensuring clinical decisions are being made using the best data possible. Therefore, critical appraisal tools are useful to evaluate study quality and to minimize bias within a published (or submitted) paper, as well as their early usefulness in designing and executing research studies. Research on assessing clinical pharmacokinetic studies to date has focused on reporting guidelines for these studies such as the ClinPK Statement, which offers excellent criteria to assess for the presence of required elements within a manuscript.[6] Reporting checklists, however, are not intended to facilitate critical appraisal of a study. A study may contain required aspects for reporting but may not meet expected quality standards. Furthermore, reporting checklists do not assess important dimensions of quality, which relate to the study design, conduct, analysis, clinical relevance and result validity.[1] While much is known about quality of clinical studies in general, these dimensions may consist of many categories or items that may be specific to a study type, or even field of research. Quality markers for randomized controlled trials, for example, may not be relevant or all encompassing for clinical pharmacokinetic studies. Tailored critical appraisal tools may therefore assist appraisers to focus their analysis on the most relevant aspects of study design, results and reporting. Before an appraisal tool aimed at assessing the quality of conduct of a study can be developed, relevant quality markers of the intended study type must be identified. Building on the work of the previously published reporting checklist, the aims of this systematic review were to create an inventory of quality markers intended for the appraisal of clinical pharmacokinetic studies and to categorize identified markers into associated domains of study quality.

2 | METHODS

2.1 | Protocol development

A protocol was developed using the principles of the Cochrane handbook.[7] The approach and eligibility criteria of the systematic review to answer the research question were predefined and reported in the protocol, which was registered and published in PROSPERO [registration number CRD42018094571].[8]

2.2 | Selection criteria

Articles, including primary studies, systematic reviews, reviews, organizational reports and guidelines, were included in this systematic review. An article was eligible for inclusion if any aspect of the trial's quality relating to study design, conduct, and analysis, clinical relevance, quality of reporting, or result validity were discussed. Articles were limited to those reported in English on human subjects only. Cell-based and animal-based pharmacokinetic studies were excluded.

2.3 | Data sources and search strategy

A search of MEDLINE (1946–Sep 2020), EMBASE (1974–Sep 2020), Cochrane database of systematic reviews, Google and Google Scholar was conducted independently by two investigators to ensure quality and optimization of the results. The following search terms were used and combined using the following Booleans: ("Pharmacokinetics" OR "Pharmacokinet*" OR "Clin*Pharmacokinet*" OR "Population pharmacokinetic") AND ("guidelines as topic" OR "Report*" OR "guideline*" OR "Evidence-based practice" OR "Appraisal tool*" OR "Checklist" OR "Scale") AND ("Quality indicators, healthcare" OR "Quality"). In Embase, the following MeSH terms were used: "Pharmacokinetics", "population pharmacokinetics", "practice guideline", "evidence based practice", "appraisal tool*", "checklist", "scale", "health care quality", "quality" were also included in the search. In MEDLINE, MeSH terms were exploded where appropriate. Additionally, keywords including "Pharmacokinetics", "Pharmacokinet*", "clin* pharmacokinet*", "population pharmacokinetic", "practice

guideline", "report* guideline*", "evidence based practice", "appraisal tool*", "checklist", "scale", "health care quality", "quality" were also included in the search. In MEDLINE, the MeSH terms were "Pharmacokinetics", "Guidelines as topic", "Quality indicators, healthcare". Keywords including "Pharmacokinetics", "Pharmacokinet*", "Clin*Pharmacokinet*", "Population pharmacokinetic", "Report* guideline*", "Evidence-based practice", "Appraisal tool", "Checklist", "Scale", "Quality" were also included in the search. Reference lists of the included articles were searched manually to include other relevant articles that were not identified while conducting the systematic search.

2.4 | Selection of studies for inclusion

All identified articles were combined, and duplicates removed using ENDNOTE (Clarivate Analytics). Two investigators independently reviewed the title and the abstract of identified studies against the pre-determined inclusion criteria. Discrepancies for inclusion were resolved through discussion or by consulting a third investigator. Full text articles were then extracted to assess their eligibility to be included.

2.5 | Data extraction

A data extraction tool was developed to extract data from included studies. Information included: author, journal, title, year, categories and subcategories of quality markers. Categories included different sections of a manuscript including abstract, introduction/background, methodology, results, discussion and conclusion. Subcategories included subsections within a category section of the article. An example of this would be the subcategory sampling under the category methodology. Identified quality markers within each subcategory were listed along with the description used to identify the quality marker with each subcategory. Data for analysis were extracted by one investigator and verified by another.

3 | RESULTS

3.1 | Included articles and characteristics

Search results, including reasons for exclusion, are provided in Figure 1. A total of 17 papers were included for extraction of quality markers. Articles included two original article about assessing the quality of reporting of clinical pharmacokinetics studies,[6,9] one systematic review,[10] one mini-review,[11] two organizational reports,[12,13] nine reviews[14-22] and two guidelines.[23,24] The included articles discussed the quality markers pertaining to retrospective and prospective clinical pharmacokinetic studies, bioequivalence studies, as well as population pharmacokinetic studies.

Quality markers encompassed 19 subcategories and were most frequently identified within the subcategories of methods and results, 15 and 11 papers, respectively. The final list of quality markers is given in Table 1. A detailed list with explanations is provided as a Appendix S1.

4 | DISCUSSION

The aim of this systematic review was to create an inventory of recognized quality markers for clinical pharmacokinetic studies. This was accomplished by extracting data from different models of clinical pharmacokinetic studies, including retrospective and prospective clinical pharmacokinetic studies, population pharmacokinetic studies, bioequivalence studies and drug interaction studies. In summary, 35 quality markers were identified across eight categories/dimensions: title, abstract, introduction, methods, results, discussion, conclusion and others (Table 1). The category with the most identified quality markers was methods. Some of the identified quality markers in this systematic review were comparable to those addressed in the CONsolidated Standards Of Reporting Trials (CONSORT 2010) guideline for randomized controlled trials[25] yet many were unique to clinical pharmacokinetic studies. These findings support the notion that an appraisal tool specific for clinical pharmacokinetic studies is warranted.

A major finding from this review is that the published literature supports appraisal of quality markers specific to clinical pharmacokinetic studies. These include examples such as study design, pharmacokinetic modelling, appraising the used apparatus and population pharmacokinetic model validation. Despite also identifying many quality markers that can be extrapolated across research fields and study designs, it is important for any potential tool to consider those markers specific to clinical pharmacokinetics. Sampling strategy including sampling site, sampling interval and sampling schedule, for example, may greatly influence the representation of the delivered concentration of the medication to the effect site. Additionally, interacting covariates was also identified that could have potential implications for affecting the pharmacokinetic parameters. This will help in determining the subgroup of patients who need specific dosing recommendations.

The findings of this systematic review must be considered in light of the previously published ClinPK Statement reporting guideline.[6] As discussed previously, this checklist is meant to determine whether a manuscript includes information about each included component but does not intend to determine how well or to what extent each component was completed. Although many identified items crossed over with the ClinPK Statement, others were identified that may be more meaningful for appraisal. Some of these include the study design subcategory, which is highly essential to be appropriately selected by researchers to accept the published results of their study. Additionally, appeasing the provided details of the used analytical method such as chromatography system, detection instrument, assay characteristics and

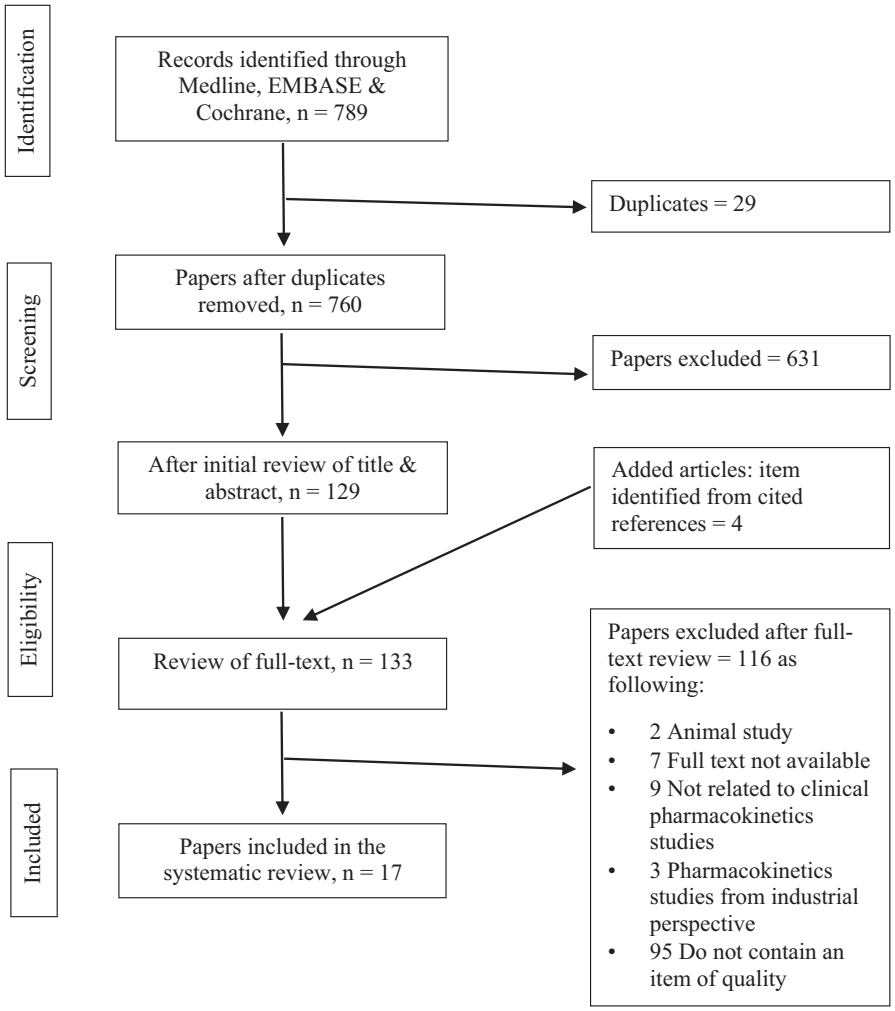

FIGURE 1 Flowchart showing literature search and articles selection

validation method is highly crucial because this will help end-users to determine whether the process is replicable and was done appropriately. Furthermore, the importance of explaining how the sample size was calculated and if this sample size is sufficient is highly essential to be appraised as this will affect the generalizability of the produced data. Moreover, there was detailed information provided in Table 1 and Appendix S1 below each subcategory to describe the element that should be present to consider it of high quality.

This review has some limitations that should be addressed. Firstly, the search strategy included terms related to quality, which may not have been stated clearly in the title of the article, the MeSH terms or keywords when it was indexed in the search engines utilized in this review. Therefore, some studies were likely missed and not included in the final list of studies included in this systematic review. As a result, the method of sample preparation was not identified as a quality marker. The method of sample preparation aids end-users to determine essential information about the integrity of the measured drug or metabolite. Additionally, it also provides insights into other critical pharmacokinetic parameters such as protein binding. Another limitation of this study was that our means of data extraction was not piloted or validated to ensure that quality markers were extracted in a comprehensive manner. While data extraction was performed by one investigator, any uncertainty was discussed openly with the research team. Finally, the results of this systematic review provide a comprehensive inventory of what is thought to represent quality markers from published literature. In the current form, the list should not be used as an appraisal tool but may inform discussion of study quality and future consideration for tool development.

5 | WHAT IS NEW AND CONCLUSION

Critical appraisal is an important process that aids in evaluating the quality of published literature. Ability to appraise articles may also foster successful application of knowledge gained from the literature to practice. In this systematic review, an inventory of quality markers was identified that encompassed both general aspects of study design, as well as specific considerations for clinical pharmacokinetic studies. These quality markers can help readers, including manuscript authors and journal editors, of clinical pharmacokinetic literature better understand and stratify high-quality research in this area of practice. Furthermore, these quality markers can be used to develop a critical appraisal tool for clinical pharmacokinetic studies.

TABLE 1 Quality markers identified from the included studies in the systematic review

Domains	Quality markers
Title	• Name of the analysed medication • Patient population
Abstract	• Objectives • Methods • Results of primary objectives • Conclusion
Background	• Introduction about the analysed drug • Rational • Goals/ objectives
Methods	• Study design o Randomization o Allocation concealment o Blinding o Monitoring plan o Patient flow diagram o Intervention and comparator (if applicable) o Inclusion and exclusion criteria o Study setting o Follow-up plan • Stating study endpoints • Sampling strategy o Sampling site o Sampling schedule o Sampling interval o Number of samples • Storage conditions • Description and justification of the used Population PK model • Validation of the Population PK model • Description of the used apparatus (Chromatography) • Equations of different PK parameters • Weight metrics used in pharmacokinetic calculation • Method used to estimate: o Area under the curve (AUC) o Area under the first moment curve (AUMC) • Identification of interacting covariates • Ethical consideration • Applied statistical methods o Level of statistical significance o Sample size calculations o Software
Results	• Participants baseline characteristics • Quantification of outliers • Quantification of missing data • Patient flow diagram • Documenting: o Variables which cause Intra and inter-patients variability o Essential PK parameters o PK results through using measure of precision • Tables and graphs that show o Development of the key model
Discussion	• Summary of the findings • Comparison to similar studies • Study limitations and strengths • Future research
Conclusion	• Consistent with the identified results
Others	• Funding resources • Conflict of interest.

CONFLICT OF INTEREST

Alaa Soliman, Shane Pawluk, Kyle Wilby and Ousama Rachid have no conflicts of interest that are relevant to the content of this study.

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DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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