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ORIGINAL RESEARCH ARTICLE

Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement

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Abstract

Background and Objective Transparent reporting of all research is essential for assessing the validity of any study. Reporting guidelines are available and endorsed for many types of research but are lacking for clinical pharmacokinetic studies. Such tools promote the consistent reporting of a minimal set of information for end users, and facilitate knowledge translation of research. The objective of this study was to create a guideline to assist in the transparent and complete reporting of clinical pharmacokinetic studies.

Methods Preliminary content to be considered was identified from a systematic search of the literature and regulatory documents. Stakeholders were identified to participate in a modified Delphi exercise and a virtual meeting to generate consensus for items considered essential in the reporting of clinical pharmacokinetic studies. The proposed checklist was pilot tested on 100 recently published clinical pharmacokinetic studies. Overall and itemized compliance with the proposed guidance was determined for each study.

Results Sixty-eight stakeholders from nine countries consented to participate. Four rounds of a modified Delphi survey and a series of small virtual meetings were required

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to generate consensus for a 24-item checklist considered to be essential to the reporting of clinical pharmacokinetic studies. When applied to the 100 most recently published clinical pharmacokinetic studies, 45 were determined to be compliant with at least 80 % of the checklist items. Explanatory text was prepared using examples of compliant reporting from these and other relevant studies.

Conclusions The reader's ability to judge the validity of pharmacokinetic research can be greatly compromised by the incomplete reporting of study information. Using consensus methods, we have developed a tool to guide transparent and accurate reporting of clinical pharmacokinetic studies. Endorsement and implementation of these guidelines by researchers, clinicians and journals would promote more consistent reporting of these studies and allow for better assessment of utility for clinical applications.

Key Points

Incomplete study reporting can lead to misinterpretation and compromised generalizability of study findings.

Compliance with ClinPK reporting guidelines will promote transparent and complete reporting of clinical pharmacokinetic studies.

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1 Introduction

Evidence-based medicine (EBM), which involves reading, interpreting, critically appraising, consolidating, and then applying knowledge obtained from primary research to patient care, has become a cornerstone of practice in recent years [1]. In order to practice EBM effectively, the clinician must be able to access complete and adequately described primary research. Information that is omitted or reported inaccurately, incompletely, unclearly, or inconsistently, can greatly affect the ability of clinicians to appraise the validity and applicability of study results to their patients. Guidelines have been developed to facilitate reporting of most types of published studies, including the CONsolidated Standards Of Reporting Trials (CONSORT 2010) guideline for randomized controlled trials and the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for systematic reviews [2, 3]. However, there are no such guidelines for published clinical pharmacokinetic studies. Most clinical pharmacokinetic studies aim to observe and measure the disposition of a drug administered to a human. Sequential sampling of relevant body fluids or tissues for quantitative measurement of a drug (or drugs) are modeled over time to describe their absorption, distribution, metabolism, and excretion [4]. To date, only one systematic review has examined the reporting quality of pharmacokinetics studies [5]. This review of pharmacokinetic studies of antibiotics in patients with sepsis receiving continuous renal replacement therapy (CRRT) found that none of the trials they identified reported all the criteria deemed essential for readers to adequately interpret the results. The authors also noted that basic pharmacokinetic parameters were reported in only 80 % of studies. We sought to create a reporting guideline named ClinPK to facilitate the transparent and complete reporting of clinical pharmacokinetic studies, thereby assisting researchers conducting such studies and increasing the usability of their results by clinicians and researchers. The objective of this study was to develop a checklist of the minimum number of essential items for reporting of clinical pharmacokinetic studies.

2 Methods

The methodology was developed by a steering committee that included members with a variety of expertise, ranging from developing reporting guidelines to conducting clinical pharmacokinetic studies. Reporting guideline development followed a structured methodology, as proposed by Moher et al. [6] which included reviewing the literature, identifying stakeholders, conducting a Delphi exercise to solicit opinions about items worthy of inclusion, and holding

virtual meetings of participants. A proposed guideline was developed and piloted, as was explanatory text [6]. Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

2.1 Literature Review to Develop Preliminary Reporting Items

Preliminary items considered to be potentially relevant to the transparent and complete reporting of clinical pharmacokinetic studies were identified from various sources using a systematic approach. This included the review of regulatory documents from the US FDA, the European Medicines Agency (EMA), Health Canada, and other relevant guidance documents [7–11]. Items were categorized according to their relevance to the sections of a traditional research report (i.e. title/abstract, background/introduction, methods, and results).

2.2 Selection of Participants

Stakeholders, defined as content experts and/or those involved in pharmacokinetic research, education, or clinical application, were systematically identified and invited to participate in this study as expert panellists. Purposeful sampling of participants via three different methods was used to minimize selection bias and have broad representation of stakeholders. Clinical researchers, identified as corresponding authors of clinical pharmacokinetic studies published in English between January 2011 and November 2012, were systematically identified from the MEDLINE, EMBASE, and International Pharmaceutical Abstracts databases using the terms 'clinical pharmacokinetic*' or 'population pharmacokinetic*'. Second, presenters of pharmacokinetic topics at two international conferences—the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics in 2011, and the World Congress on Basic and Clinical Pharmacology in 2010—were identified for participation. Finally, contributing authors to the 4th edition of Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications were approached [4].

Potential participants were emailed a 'pre-survey invitation' letter explaining the purpose of the study and measures used to ensure confidentiality, as well as requesting their participation. To be eligible, participants declared themselves as stakeholders or content experts and provided their informed consent. No incentive or compensation was offered to participants.

2.3 Modified Delphi Survey

The modified Delphi process was used to achieve consensus amongst participants regarding the items considered essential for inclusion in reporting guidelines [12]. Serial surveys were administered electronically via SurveyMonkey® (Palo Alto, CA, USA) where each iteration was refined based on the previous one. Panellists were asked to review the preliminary list of potential items relevant to the transparent reporting of clinical pharmacokinetic studies. Participants were then asked to decide if the item was considered essential for inclusion in the reporting tool by selecting one of 'yes', 'no', or 'unsure'. An item was considered essential if it was deemed necessary for readers to assess the generalizability and external validity of the study findings. For each item, panellists were asked to rank its importance using a 5-point Likert scale (1 = not important, 5 = very important), with comments for clarification. Finally, panellists were given the opportunity to nominate additional items for consideration. For each subsequent iteration of the survey, participants were given their answers from the previous iteration and the blinded aggregate responses from the entire group. A minimum of three rounds of the survey (administered 6 weeks apart) were planned with the possibility of more if consensus could not be reached. Inclusion of an item required 80 % consensus among respondents. If substantial divergence in scoring occurred, comments were reviewed and the item was re-worded for clarification. If consensus was still not met, the item was excluded. All communication occurred via email. Participants were given 4 weeks to complete each questionnaire, with three subsequent reminder emails. Participant anonymity and confidentiality were ensured, with individual responses only available to the survey moderator (MH).

2.4 Virtual Meeting via Serial Small Group Teleconferences

A virtual meeting was planned after three rounds of the Delphi survey. All participants were invited but participation was voluntary. Small group teleconferences involving up to five participants and one investigator (SK) were conducted to allow for discussion, address concerns and make revisions to the checklist. All sessions were recorded and facilitated by a moderator following a predetermined meeting agenda. Adjustments made during the teleconferences were substantial; therefore, a fourth round of the Delphi survey was required to obtain consensus for modified and new items.

2.5 Pilot Testing and Development of Explanation and Elaboration Statement

The final checklist was applied to 100 recent clinical pharmacokinetic studies to test usability of the tool while evaluating the reporting of published studies. Ovid

MEDLINE was searched retrospectively from 11 July 2014 using the search term 'pharmacokinetic$' for clinical trials in humans published in English. Studies of less than five participants were excluded. Abstracts and then full manuscripts were reviewed for inclusion criteria until a sample of 100 was reached. Manuscripts were examined for the presence or absence of each item in the proposed checklist. Applying the checklist and data extraction were performed in triplicate (by AL, MH, and SK) for the first ten articles and then every subsequent tenth one. Conflicts were resolved in person by consensus. Compliance with the overall tool and each individual item were collated in Excel® (Version 14.1.0, 2011; Microsoft Corporation, Redmond, WA, USA) and reported as proportions.

Explanatory text was created using examples of exemplary reporting for each item from the 100 aforementioned clinical pharmacokinetic studies. Where appropriate examples were not found, examples were sought from older publications. The purpose of this guideline is to support and demonstrate each item in the checklist as selected via the Delphi process and virtual meetings of panellists.

3 Results

3.1 Expert Panellists

Two hundred and forty-one potential participants were identified, 187 of whom were invited to participate after the initial screening for public contact information. In total, 68 participants identified themselves as stakeholders (electronic supplementary Table S1). There were an even distribution of researchers and knowledge users, and representation from nine different countries, while the majority of participants (78 %) were from Canada and the US.

3.2 Delphi Survey and Virtual Meeting Results

Response rates for the first three rounds of the Delphi survey were 68/68 (100 %), 64/68 (94 %), and 54/68 (79 %), respectively. Only two surveys had missing data. Twenty-eight panellists participated in the small group teleconferences. The groups ranged from three to five members, not including the moderator and one investigator (SK). The fourth iteration of the survey that followed the virtual meetings had a response rate of 50/68 (74 %).

Nineteen items identified from the literature search and review of regulatory documents were included in the first round of the Delphi survey (Fig. 1). During the four Delphi rounds and teleconferences, seven items were added based on stakeholder suggestions, and six items were removed due to lack of consensus, or collapsed into other items. The final checklist included 24 items that met consensus. Almost all items were reworded for clarity and face validity. Items that met criteria for inclusion in the final checklist with corresponding ratings of importance are reported in Table 1. Items that were ultimately rejected due to lack of consensus are shown in Table 2. With respect to the importance of items, eight were rated by more than 50 % of panellists as 'very important', and all 24 items were rated by more than 70 % of panelists as 'important' or 'very important'.

3.3 Pilot Testing

One hundred recently published clinical pharmacokinetic studies were reviewed for completeness of reporting using the ClinPK checklist. Seventy of these studies were prospective in nature. Fifty-nine studies were classified as traditional pharmacokinetic studies and 41 as population pharmacokinetic studies. Thirteen studies evaluated drug interactions, while seven evaluated extracorporeal drug removal. The median number of study participants was 38, with a range of 7–3,642.

Overall compliance with the proposed reporting tool was greater than 80 % for 45 of the 100 papers when items deemed 'not applicable' were removed from the denominator (Table 3). Compliance was highest for prospective traditional (i.e. non-population-based) pharmacokinetic studies. Compliance with individual checklist items is reported in Table 4. Non-compliance was most commonly related to data elements excluded from the study abstract, co-administration of interacting drugs or food, description of body fluid or tissue sampling, mathematical formulas utilized, reporting of body weight metrics, and specifics of extracorporeal drug removal variables (items 2, 7, 9, 13, 14, 17, and 20). Specific examples of compliant reporting for each of the items on the ClinPK checklist are provided in electronic supplementary Table S2. No substantive changes to the checklist were deemed necessary following pilot testing. The final ClinPK checklist is provided in Table 5.

3.4 Explanation and Elaboration

The ClinPK checklist is divided into six sections: title/abstract, background, methods, results, discussion/conclusion, and other information. For each group of related items within a section, a rationale for their inclusion in the checklist and, furthermore, importance in reporting pharmacokinetic studies, is provided.

Item 1 The title identifies the drug(s) and patient population(s) studied.

Item 2 The abstract minimally includes the name of the drug(s) studied, route of administration, population in

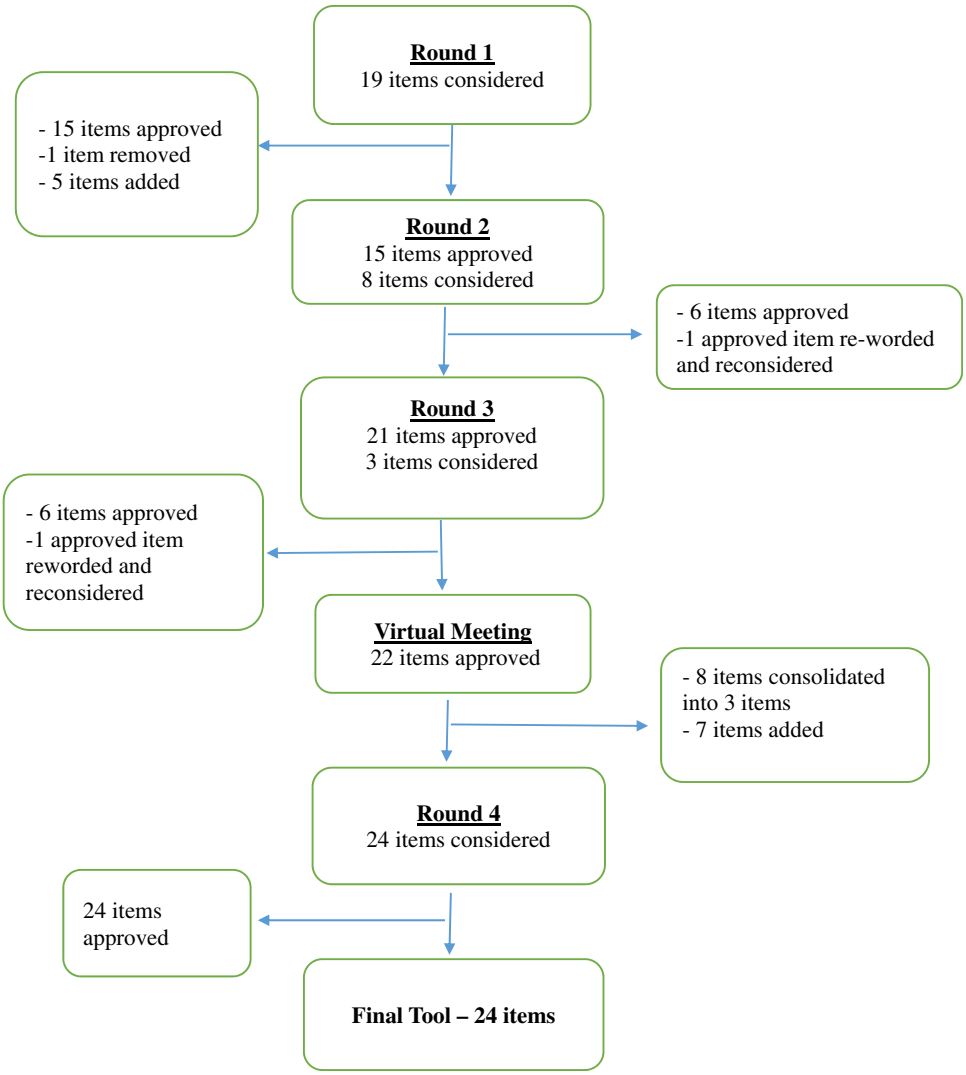

Fig. 1 Delphi survey flow diagram

whom it was studied, sample size, and results of the primary objective and major clinical pharmacokinetic findings.

Rationale: The primary reason for providing this level of detail in the title and abstract is to ensure proper indexing in searchable databases such as MEDLINE. Quite often, the title and abstract are the only publicly available information. Ideally, the title and abstract should provide enough detail about the study to provide readers and researchers with a sense of relevance to their directed search or interest. In our review, the drug was always identified in the title but the population in which it was studied was missing 20 % of the time. In 45 % of cases, the most common item missing in the abstracts reviewed was the route of administration. Quite often, the drugs in question are available for administration via one route only but not all readers may be aware of this.

Item 3 Pharmacokinetic data (i.e. absorption, distribution, metabolism, excretion) that are known and relevant to the drugs being studied are described.

Item 4 An explanation of the study rationale is provided.

Item 5 Specific objectives or hypotheses are provided

Rationale: The background or introduction provides context for the reader. The rationale for the study should include a discussion of what new information will be generated and how it will add to existing knowledge. Authors should be as precise and explicit as possible when stating their study objectives so readers can quickly assess the scope of the study and its potential applicability to their interest. Compliance with items 3, 4 and 5 in our review was considered very good (87, 95, and 98 %, respectively).

Item 6 Eligibility criteria of study participants are described.

Rationale: The external validity of clinical pharmacokinetic studies hinges on the types of patients enrolled in the study. Not only does it minimize the risk of selection bias but it also allows the reader to appraise the applicability of the findings. Authors should report eligibility criteria with as little ambiguity as possible.

Table 1 ClinPK checklist with consensus rate and importance rating by expert panellists

Checklist item		Consensus [*N* (%)][a]	Importance rating[b] [median (IQR)]
Title/abstract			
1	The title identifies the drug(s) and patient population(s) studied	66/68 (97)	5 (1)
2	The abstract minimally includes the name of the drug(s) studied, route of administration, population in whom it was studied, and results of the primary objective and major clinical pharmacokinetic findings	56/64 (88)	5 (0)
Background			
3	Pharmacokinetic data (i.e. absorption, distribution, metabolism, excretion) that are known and relevant to the drugs being studied are described	48/50 (96)	5 (1)
4	An explanation of the study rationale is provided	50/50 (100)	5 (0)
5	Specific objectives or hypotheses are provided	50/50 (100)	5 (1)
Methods			
6	Eligibility criteria of study participants are described	48/50 (96)	5 (0)
7	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described	68/68 (100)	5 (1)
8	Drug preparation and administration characteristics, including dose, route, formulation, infusion duration (if applicable), and frequency are described	50/50 (100)	5 (0)
9	Body fluid or tissue sampling (timing, frequency, and storage) for quantitative drug measurement are described	65/68 (96)	5 (1)
10	Validation of quantitative bioanalytical methods used in the study are referenced or described if applicable	68/68 (100)	5 (1)
11	Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first, or mixed order)	49/50 (98)	5 (0)
12	For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described	63/68 (93)	5 (1)
13	Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced	58/68 (85)	5 (1)
14	The specific body weight used in drug dosing and pharmacokinetic calculations are reported (i.e. ideal body weight vs. actual body weight vs. adjusted body weight)	50/50 (100)	5 (0)
15	Statistical methods, including software used, are described	50/50 (100)	5 (0)
Results			
16	Study withdrawals or subjects lost to follow-up (or lack thereof) are reported	54/64 (84)	4.5 (1)
17	Quantification of missing or excluded data is provided if applicable	62/68 (91)	5 (1)
18	All relevant variables that may explain inter- and intrapatient pharmacokinetic variability (including age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variance	68/68 (100)	5 (1)
19	Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95 % confidence intervals)	50/50 (100)	5 (0)
20	Studies in patients receiving extracorporeal drug removal (i.e. dialysis) should report the mode of drug removal, type of filters used, duration of therapy, and relevant flow rates	46/50 (92)	5 (1)
21	In studies of drug bioavailability comparing two formulations of the same drug, *F*, AUC, C_{max}, and t_{max} should be reported	55/64 (86)	5 (1)
Discussion/conclusion			
22	Study limitations describing potential sources of bias and imprecision, where relevant, should be described	49/50 (98)	4.5 (1)
23	The relevance of study findings (applicability, external validity) is described	46/50 (92)	4.5 (1)
Other information			
24	Funding sources and conflicts of interest for the authors are disclosed	57/64 (89)	5 (1)

AUC area under the concentration-time curve, *BMI* body mass index, C_{max} maximum concentration, *F* bioavailability, *IQR* interquartile range, t_{max} time to maximum concentration

[a] The denominator varies as it reflects the total number of respondents for each item in the round in which the item was included

[b] Likert rating: 5 = very important, 4 = important, 3 = neutral (neither important or unimportant), 2 = somewhat unimportant, 1 = not important

Table 2 Items excluded from the ClinPK checklist

Item	Consensus rate [*N* (%)]	Action
Sample size justification is described, including any assumptions made to calculate sample size	33/54 (61)	Excluded after round 3
Adverse events (or lack thereof) are reported, including the method of capturing adverse events	37/64 (65)	Excluded after round 3
Baseline measurement of drug concentration (i.e. time zero) is reported prior to drug administration for prospective studies	51/68 (75)	Collapsed into item #9
Drug preparation methods and packing materials are described, including diluents and final concentrations of IV and oral solutions	55/64 (87)	Collapsed into item #6
Studies of drug metabolism should consider both parent compound and, minimally, active metabolite(s)	59/68 (87)	Collapsed into item #3
Studies of drug metabolism should describe all metabolic pathways, including organ-independent metabolism	45/68 (66)	Collapsed into item #3
Studies describing drug distribution should report relevant protein binding	59/68 (87)	Collapsed into item #3
Drug interaction studies must describe all potential pathways impacting drug disposition, including organ-independent pathways (e.g. extrahepatic metabolism) and transporter influences, when known and applicable	59/68 (87)	Collapsed into item #3
Pharmacokinetic modeling software (if used) is reported	66/68 (97)	Collapsed into item #11

IV intravenous

Table 3 Overall compliance of 100 recently published clinical pharmacokinetic studies with the ClinPK checklist

Compliance (% of checklist)	All studies [*n* = 100]	Traditional PK studies [*n* = 59]	Population PK studies [*n* = 41]	Retrospective studies [*n* = 30]	Prospective studies [*n* = 70]
80–100	45 (45)	30 (51)	15 (37)	8 (27)	37 (53)
60–79	43 (43)	20 (34)	23 (56)	17 (57)	26 (37)
40–59	12 (12)	9 (15)	3 (7)	5 (17)	7 (10)
0–39	0	0	0	0	0

Values are expressed as number of studies (%). Checklist items deemed 'not applicable' were not included in the denominator for individual studies when calculating proportions

PK pharmacokinetic

Item 7 Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within the study is described.

Rationale: Interactions with other drugs, dietary supplements, or food are an important consideration in the pharmacokinetics of many drugs. Researchers must be diligent in their efforts to minimize variability in pharmacokinetic studies. For example, bioavailability studies often have small sample sizes, use homogeneous study populations, control for diet (fed or fasting), and restrict concomitant drugs. Authors should convey these efforts in their inclusion criteria or describe the frequency of potential interactions. The reader cannot assume that omission of documentation about potential drug interactions means that they did not occur or were actively avoided. This was poorly reported in our review of the literature (56 %), with the timing of enteral drug administration relative to food being the most underreported.

Item 8 Drug preparation and administration characteristics, including dose, route, formulation, infusion duration (if applicable) and frequency are described.

Rationale: Among and within countries, drug manufacturers and formulations of the same drug may differ enough to affect the preparation, administration, or disposition of the drug. Even within the same country, different manufacturers and formulations of the same drug exist. For example, acetaminophen is produced by several manufacturers in Canada as regular-release tablets, quick-release capsules, slow-release capsules, chewable tablets, and suspension. In some countries, it is even available for intravenous injection. Furthermore, there are multiple dosing strategies and administration techniques that can influence the pharmacokinetic profile of acetaminophen. Accurate description of drug preparation and administration are essential to the external validity of such studies.

Item 9 Body fluid or tissue sampling (timing, frequency, and storage) for quantitative drug measurement is described.

Rationale: The timing and number of samples drawn for study drug quantification will directly influence the validity of pharmacokinetic modeling [13]. For example, a sample measurement immediately prior to drug administration

Table 4 Itemized compliance with ClinPK

Item[a]	Compliance	
	Count[b]	%
Title/abstract		
1	80/100	80
2	49/100	49
Background		
3	87/100	87
4	95/100	95
5	98/100	98
Methods		
6	94/100	94
7	55/98	56
8	76/99	77
9	47/96	49
10	86/99	87
11	89/96	93
12	44/44	100
13	56/100	56
14	22/99	22
15	83/100	83
Results		
16	51/77	66
17	54/98	55
18	92/100	92
19	90/100	90
20	1/7	14
21	10/12	83
Discussion/conclusion		
22	71/100	71
23	99/100	99
Other information		
24	85/100	85

[a] See Table 1 for an explanation of each item

[b] The denominator denotes the number of studies for which the item was applicable

(time zero) would be necessary to demonstrate that baseline drug concentrations are zero or describe baseline concentrations in pragmatic study designs. Similarly, samples drawn before steady state might produce a different pharmacokinetic profile than those drawn at steady state. The purpose of reporting guidelines is not to address issues of study conduct or risk of bias but rather to ensure that the reader has enough information available to them to make this assessment.

Item 10 Validation of quantitative bioanalytical methods used in the study are referenced or described if applicable.

Item 11 Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first, or mixed order).

Item 12 For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described.

Rationale: There is not one universally accepted bioanalytical or modeling method for all pharmacokinetic studies. In reality, there are many different approaches, each with their own assumptions and limitations. This tool is meant to increase the accurate reporting of these methods so the reader at least has the information to evaluate or compare the methodological rigor. Referencing or describing an analytical or modeling method also ensures that methods can be reproduced by others looking to confirm the results or apply the methods in another context. Decisions made regarding pharmacokinetic modeling (i.e. compartmental vs. non-compartmental approaches, parametric vs. non-parametric population pharmacokinetic modeling) should be described [14, 15]. Choosing covariates for a population pharmacokinetic model should be based on biologic plausibility a priori and described as such. Although this is the only item in the tool specifically directed to population pharmacokinetic studies, it must be acknowledged that this tool may not meet all the reporting needs of more complex or less frequently encountered study designs [16, 17].

Item 13 Formulas for calculated variables (such as creatinine clearance, body surface area, area under the concentration-time curve [AUC], and adjusted body weight) are provided or referenced.

Rationale: There can be numerous methods or formulas to calculate a single variable. For example, creatinine clearance or glomerular filtration rate is most commonly estimated using the Cockroft–Gault equation or the Modification of Diet in Renal Disease (MDRD) formula [18, 19], respectively, but there are variations of these equations and 46 other prediction equations described in the literature [20]. Since the products of these different formulas can be highly variable, and considering that drug dosing in renal failure is often based on thresholds of creatinine clearance or renal function, it is essential that authors disclose the formulas used in these calculations.

Item 14 The specific body weight used in drug dosing and pharmacokinetic calculations are reported (i.e. ideal body weight vs. actual body weight vs. adjusted body weight).

Rationale: From our review of reporting quality in clinical pharmacokinetic studies, only 22 % of publications explicitly stated which weight was used in drug dosing. Presumably when authors write 'body weight', the reader is to assume the author is referring to 'actual body weight', but improved clarity would negate the reader's need to make assumptions. Size or weight descriptors used in

Table 5 ClinPK checklist of information to be included when reporting a clinical pharmacokinetic study

	Checklist Item	
	Title/Abstract	**Reported on Page Number**
1	The title identifies the drug(s) and patient population(s) studied.	
2	The abstract minimally includes the name of the drug(s) studied, the route of administration, the population in whom it was studied, and the results of the primary objective and major clinical pharmacokinetic findings.	
	Background	
3	Pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion) that is known and relevant to the drugs being studied is described	
4	An explanation of the study rationale is provided	
5	Specific objectives or hypotheses is provided	
	Methods	
6	Eligibility criteria of study participants are described	
7	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described.	
8	Drug preparation and administration characteristics including dose, route, formulation, infusion duration (if applicable) and frequency are described.	
9	Body fluid or tissue sampling (timing, frequency and storage) for quantitative drug measurement is described.	
10	Validation of quantitative bioanalytical methods used in the study are referenced or described if applicable.	
11	Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first or mixed order).	
12	For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described.	
13	Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced.	
14	The specific body weight used in drug dosing and pharmacokinetic calculations are reported (i.e., ideal body weight vs. actual body weight vs. adjusted body weight)	
15	Statistical methods including software used are described	
	Results	
16	Study withdrawals or subjects lost to follow-up (or lack thereof) are reported.	
17	Quantification of missing or excluded data is provided if applicable.	
18	All relevant variables that may explain inter- and intra-patient	
	pharmacokinetic variability (including: age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variance.	
19	Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95% confidence intervals)	
20	Studies in patients receiving extracorporeal drug removal (i.e., dialysis) should report the mode of drug removal, type of filters used, duration of therapy and relevant flow rates.	
21	In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, Cmax (maximal concentration) and Tmax (time to maximal concentration) should be reported.	
	Discussion/Conclusion	
22	Study limitations describing potential sources of bias and imprecision where relevant should be described	
23	The relevance of study findings (applicability, external validity) is described	
	Other Information	
24	Funding sources and conflicts of interest for the authors are disclosed.	

AUC area under the concentration-time curve, *BMI* body mass index, C_{max} maximum concentration, *F* bioavailability, t_{max} time to maximum concentration

dosing calculations and mathematical modeling can have a significant impact on estimated pharmacokinetic parameters [21]. Authors are encouraged to explicitly state the weight metric used in drug dosing and pharmacokinetic calculations to ensure that readers applying weight-based dosing recommendations from these studies are doing so correctly.

Item 15 Statistical methods, including software, are described.

Rationale: Similar to items 10–12, statistical analytic methods should be predetermined, at least for the primary objective. Some analyses may be initiated after generating the data, and the authors should describe which analyses were carried out in a post hoc fashion. Description of statistical methods should be detailed enough for readers to not only appreciate what was done but also to compare statistical methods between studies. In our review of published pharmacokinetic studies, 17 % of studies did not provide sufficient detail regarding the statistical analyses.

Item 16 Study withdrawals or subjects lost to follow-up (or lack thereof) are reported.

Item 17 Quantification of missing or excluded data is provided if applicable.

Rationale: Understanding why enrolled patients were withdrawn from a study or not included in the analyses is important to evaluate the potential introduction of bias and generalizability of the study population. Similarly, it is important to explain how missing data were handled in the analysis [22, 23]. There are many reasons why data or patients might be excluded from the analysis (withdrawal of consent, errors in sampling, missed data capture), and authors should be transparent in both quantification and handling of study withdrawals and missing data.

Item 18 All relevant variables that may explain inter- and intrapatient pharmacokinetic variability (including age, sex, end-organ function, ethnicity, weight or body mass index [BMI], health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variance.

Rationale: For a given drug, there is typically wide interpatient, and often even intrapatient, variability in pharmacokinetics. While increasing the sample size is one strategy to minimize variability, researchers must balance the sample size with the associated cost and resources required. Another strategy is to be highly selective of patients (i.e. with restrictive inclusion and exclusion criteria). While this strategy is more cost effective, it can compromise the generalizability of the study. It is ultimately up to the reader to determine whether or not the study results will apply to their patient(s) by comparing the characteristics of patients enrolled with their own patient(s). It is therefore essential that authors describe the study population in as much detail as possible. In our review of published pharmacokinetic studies, this information was available to the reader in 92 % of studies but quite often it was spread out between the inclusion criteria, results, and tables. Consolidation into a table would make it easier for the reader to find this important information in one place and increase clinical utility.

Item 19 Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95 % confidence intervals).

Rationale: As described in item 18, variability between or within patients can be significant in pharmacokinetic studies, and providing measures of precision for study outcomes describes the magnitude of this variability. In the example provided in electronic supplementary Table S2, one can see that the mean half-life for metformin when taken with pantoprazole is 3.38 h [24]. However, the accompanying standard deviation of 0.69 further informs the reader that the half-life may be variable between patients. In fact, approximately two-thirds of patients will have half-lives within one standard deviation of the mean, or between 2.7 and 4.1 h.

Item 20 Studies in patients receiving extracorporeal drug removal (i.e. dialysis) should report the mode of drug removal, type of filters used, duration of therapy, and relevant flow rates.

Rationale: Drug dosing in patients with renal failure can be challenging, particularly in patients receiving various forms of renal replacement therapy (i.e. hemodialysis, CRRT). Pharmacokinetic studies that describe the clearance of drugs via these extracorporeal means are necessary to inform drug dosing in these special circumstances. However, there are several modifiable variables that contribute to drug clearance, including those listed above. Furthermore, these variables can differ between institutions and among patients. In order for the reader to properly address the relevance of a particular study, these details should be reported. Our review identified only seven studies for which this item was relevant, and only one study reported all of the relevant components related to extracorporeal drug removal. Some studies reported nothing other than the mode of drug removal. Despite the small numbers, this observation is consistent with the previously mentioned review by Li et al. [5].

Item 21 In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, C_{max} (maximum concentration), and t_{max} (time to maximum concentration) should be reported.

Rationale: Studies of drug bioavailability typically compare the extent of drug delivery from two or more formulations (i.e. oral compared with intravenous dosing, or brand name compared with generic drugs). The most important pharmacokinetic variable to report is the absorption ratio or bioavailability (absolute and/or

relative), but all of the listed parameters should be reported for comparison [25]. Typically, minimal thresholds for ratios are determined a priori and should also be reported as such.

Item 22 Study limitations describing potential sources of bias and imprecision, where relevant, are described.

Rationale: Identification and discussion of study limitations are important aspects of transparency for all scientific reporting. It is not only important to identify potential sources of bias but also to address measures taken to minimize potential bias and hypothesize as to the influence it might have on the study findings. Similarly, there may be many sources of imprecision within a study, such as small sample size, measurement error, and confounders. Authors should identify these for the reader and discuss how they might influence the interpretation of study findings.

Item 23 The relevance of study findings (applicability, external validity) is described.

Rationale: Not only should authors report the results of their study but also provide context as to how their findings contribute to what is already known on the topic. Authors are encouraged to compare their results with those of other similar studies, and comment on the generalizability of their findings. Generalizability (or external validity) refers to the extent to which the study findings can be applied in other circumstances (e.g. different patient populations, different institutions, different disease states). Since pharmacokinetic studies are often conducted in highly selective study subjects, generalizability warrants a paragraph in the discussion section of the manuscript.

Item 24 Funding sources and conflicts of interest for the authors are disclosed.

Most journals now require and publish a statement delineating the source(s) of funding and disclosing conflicts of interest. Most journals also now require a statement confirming that studies have been reviewed and approved by local Research Ethics Boards. Historically, there are many examples of conflicts of interest influencing the design of the study, statistical methods, and publication of outcomes [26]. Disclosure of conflicts of interest and the role of the funding source(s) should be described in detail.

4 Discussion

The ClinPK guidelines for the transparent reporting of clinical pharmacokinetic studies have been developed via consensus by key stakeholders. This guidance is suggested as the minimum reporting criteria required for all published clinical pharmacokinetic studies, acknowledging that different types of studies (i.e. drug interaction studies) may necessitate the reporting of additional items in order to be complete.

The ClinPK guideline is not intended to inform study conduct, but may be useful to researchers in designing research studies. Compliance with the tool will ensure that the validity of clinical pharmacokinetic studies can be assessed by the end user to determine if or how the study applies to their patient care practice.

In order to facilitate implementation, this guideline was developed in a format similar to other reporting checklists. The ClinPK guideline contains many items that are consistent with reporting guidelines, such as the CONSORT guideline for randomized clinical trials and the PRISMA guideline for systematic reviews.

Pilot testing the ClinPK checklist revealed that less than half (45 %) of the most current published pharmacokinetic studies are compliant with 80 % or more of the items in the checklist. Traditional pharmacokinetic studies (compared with population pharmacokinetic studies) and prospective studies (compared with retrospective studies) were found to have better compliance with the checklist. The items from the checklist that were identified less than 50 % of the time were related to the completeness of the abstract (item 2), fluid or tissue sampling (item 9), specific body weight metric used in dosing and pharmacokinetic calculations (item 14), and description of extracorporeal drug removal variables in relevant studies (item 20).

Although this guideline was developed with efforts to minimize bias, there are several limitations. First, clinical pharmacokinetics is a broad field that encompasses several disciplines; therefore it is likely that not every key stakeholder was invited to participate. This is an important limitation because the strength of the guidance depends on the expertise of the participants. In order to minimize this risk, we utilized multiple strategies to identify currently active researchers and users of clinical pharmacokinetic studies. The result was a broad representation of both knowledge users and researchers, albeit skewed toward the US and Canada, with relatively low representation from pharmaceutical industry. Despite this, the demographic distribution of participants would suggest that the tool is representative of the majority of stakeholders but broader representation should be considered when subsequent iterations of the tool become warranted.

It is also likely that some checklist items may not be relevant for all types of clinical pharmacokinetic studies, while others might be considered essential for specific studies. In order to minimize the amount of specialized items, the panellists were advised to consider items relevant to the majority of clinical pharmacokinetic studies from the perspective of the reader/knowledge user. Even in our review of the published literature, we encountered few bioavailability studies and studies of extracorporeal drug removal. As such, our ability to evaluate the items specific to these types of studies was less robust. Furthermore, the

current tool may not fully address the reporting needs of complex study designs, such as population pharmacokinetic studies or non-compartmental analyses [16, 17]. As with all reporting guidelines, limitations will become apparent and further modification may be warranted in subsequent iterations, particularly as this field of research progresses.

Pharmacokinetic studies not only inform the dosing and drug delivery of drug therapy but can also inform clinicians about drug interactions and drug disposition over time. However, this is true only when the study conduct is adequately described and the results are completely reported in a way that can be utilized by the end user. This issue was illustrated in a study by Li et al. in which a minimal reporting dataset for pharmacokinetic studies during renal replacement therapy was created, and then evaluated relevant studies in the literature for completeness of this information. None of the studies reviewed reported the full dataset, and many studies did not report the basic pharmacokinetic parameters such as drug volume of distribution and clearance needed to interpret CRRT studies. The study by Li and colleagues [5] highlights the need for reporting guidelines specific to pharmacokinetic studies. Not only is the ClinPK reporting guideline expected to be useful for end users of pharmacokinetic studies but it may also assist researchers in reporting their study data and findings. Using these guidelines, researchers can ensure inclusiveness of what is important to the end user. Journals that endorse and implement this guideline will also ensure that their readers and reviewers will have sufficient information to evaluate the relevance of the published papers to their practice.

5 Conclusion

The results of this modified Delphi survey have yielded a checklist highlighting the minimum reporting criteria necessary for readers to adequately evaluate pharmacokinetic studies. As the field of pharmacokinetics continues to advance, modifications and variations of this tool will be necessary to evolve with the literature and maintain its practical benefits. This guidance is expected to be important to both knowledge user and researcher as it facilitates the transparent and complete reporting of clinical pharmacokinetic studies.

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References

1. Upton D, Upton P. Knowledge and use of evidence-based practice of GPs and hospital doctors. J Eval Clin Pract. 2006;12:376–84.
2. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
3. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152:726–32.
4. Rowland M, Tozer T. Clinical pharmacokinetics and pharmacodynamics: concepts and applications. 4th ed. USA: Lippincott Williams and Wilkins; 2010.
5. Li AM, Gomersall CD, Choi G, Tian Q, Joynt GM, Lipman J. A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? J Antimicrob Chemother. 2009;64:929–37.
6. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med. 2010;7:e1000217.
7. Guideline on reporting the results of population pharamacokinetic analyses. 2007. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf. Accessed 30 Jan 2013.
8. Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. 2004. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf. Accessed 30 Jan 2013.
9. ICH guidance E6: good clinical practice. Consolidated guideline. 2004. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e6-eng.pdf. Accessed 31 Jan 2013.
10. Clinical pharmacokinetic studies of pharmaceuticals. 2001. Available at: http://www.nihs.go.jp/phar/pdf/ClPkEng011122.pdf. Accessed 30 Jan 2013.
11. Guidance for industry: population pharmacokinetics. 1999. Available at: http://www.fda.gov/cder/guidance/. Accessed 30 Jan 2013.
12. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess. 1998;2:1–4, 1–88.
13. Jonsson EN, Wade JR, Karlsson MO. Comparison of some practical sampling strategies for population pharmacokinetic studies. J Pharmacokinet Biopharm. 1996;24:245–63.
14. Gerlowski LE, Jain RK. Physiologically based pharmacokinetic modeling: principles and applications. J Pharm Sci. 1983;72:1103–27.
15. Karlsson MO, Jonsson EN, Wiltse CG, Wade JR. Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. J Pharmacokinet Biopharm. 1998;26:207–46.
16. Brendel K, Dartois C, Comets E, et al. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin Pharmacokinet. 2007;46:221–34.
17. Dartois C, Brendel K, Comets E, et al. Overview of model-building strategies in population PK/PD analyses: 2002–2004 literature survey. Br J Clin Pharmacol. 2007;64:603–12.

18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461–70.
20. Diamandopoulos A, Goudas P, Arvanitis A. Comparison of estimated creatinine clearance among five formulae (Cockroft–Gault, Jelliffe, Sanaka, simplified 4-variable MDRD and DAF) and the 24 hours-urine-collection creatinine clearance. Hippokratia. 2010;14:98–104.
21. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58:119–33.
22. Ette EI, Sun H, Ludden TM. Ignorability and parameter estimation in longitudinal pharmacokinetic studies. J Clin Pharmacol. 1998;38:221–6.
23. Keizer RJ, Zandvliet AS, Beijnen JH, Schellens JH, Huitema AD. Performance of methods for handling missing categorical covariate data in population pharmacokinetic analyses. AAPS J. 2012;14:601–11.
24. Kim A, Chung I, Yoon SH, et al. Effects of proton pump inhibitors on metformin pharmacokinetics and pharmacodynamics. Drug Metab Dispos. 2014;42:1174–9.
25. Ritschel WA. Bioavailability/bioequivalence of modified release drug delivery systems: which pharmacokinetic parameters to determine, single or multiple dose studies, pretests, conditions and other aspects. Methods Find Exp Clin Pharmacol. 1992;14:469–82.
26. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA. 2003;290:921–8.