Journal of Clinical Epidemiology 117 (2020) 126−137

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Drug−drug interaction trials incompletely described drug interventions in ClinicalTrials.gov and published articles: an observational study

Diana Jurić[a,*], Adriana Bolić[b], Shelly Pranić[c], Ana Marušić[c]

[a]Department of Pharmacology, University of Split School of Medicine, Split, Croatia
[b]Public Pharmacy PrimaPharme, Split, Croatia
[c]Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia

Accepted 16 October 2019; Published online 22 October 2019

Abstract

Objectives: The aim of the study was to evaluate the completeness of intervention description in ClinicalTrials.gov and corresponding journal articles for registered and published drug−drug interaction (DDI) trials because complete and transparent description of interventions is particularly important for DDI.

Study Design and Setting: Observational study of completed interventional trials on DDIs with up to two drugs within the Intervention registration element in ClinicalTrials.gov until October 2015. We used the Template for Intervention Description and Replication items to assess the quality of intervention description in both ClinicalTrials.gov Descriptive Information section and matching publications. Corresponding articles were identified in March 2019.

Results: The description of 1,180 drug interventions registered for 642 DDI trials mostly lacked information on the intervention provider (99.7%), adherence strategies (99.2%), procedure (83.8%), location (71.3%), and dosage form (60.7%). Generic name (82.5%), dose (70.8%), and duration of administration (65.6%) were most frequently reported. Among 51 trials that had data reported both in ClinicalTrials.gov and publication, 60.8% were in phase 1. Less than half of 96 interventions had clear and matching description of dosage form, procedure, and route of administration in both sources.

Conclusion: DDI trials did not sufficiently report components required for complete intervention description. Further improvements in ClinicalTrials.gov registration requirements, including phase 1 trials, and more stringent publishing requirements for essential data on drug interventions, are needed to prevent patient risk in clinical practice regarding concomitant medication use.

Keywords: Description of drug intervention as topic; Drug interaction; Databases; Reporting; Bias; Transparency; Trial registration

1. Introduction

Detailed and clear reporting of methodological approaches, including the study intervention, is an ethical and scientific standard [1,2] and crucial for critical evaluation of the validity of a clinical trial. Inadequate descriptions of interventions can impede the replication of a trial and its implementation in routine clinical practice, affecting both health practitioners and patients [3].

However, the quality of intervention descriptions in journal articles seems to be remarkably poor [3−7]. In the light of raising awareness, guidelines assisting in intervention descriptions have been developed to promote more adequate and consistent trial reporting [8−10].

The closest step to an appropriate form of reporting regarding trial interventions was achieved in the Template for Intervention Description and Replication (TIDieR) checklist from 2014, which is an extension of the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [9] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement

Funding: This study was supported in part by the Croatian Science Foundation, grant no. IP-2014-09-7672 "Professionalism in Health Care." The funder had no role in the design of this study, during its execution and data interpretation, and in the decision to submit the article for publication.

Conflicts of interest: The authors declare that they have no competing interests.

Ethics committee approval: Not required.

Availability of data: The datasets used and analyzed during the present study are available from the corresponding author on request.

* Corresponding author. Department of Pharmacology, University of Split School of Medicine, Šoltanska 2, Split 21000, Croatia. Tel.: +38 598 169 9321; fax: +38 521 557 811.

E-mail address: diana.juric@mefst.hr (D. Jurić).

https://doi.org/10.1016/j.jclinepi.2019.10.002

What is new?

Key findings

- The quality of intervention descriptions using the Template for Intervention Description and Replication (TIDieR) in drug−drug interaction (DDI) trials was found to be poor in ClinicalTrials.gov and corresponding publications. We identified discrepancies between two sources for DDI trials with up to two drug interventions registered in ClinicalTrials.gov, which were mostly in phase 1.

What this adds to what was known?

- Despite DDIs could precipitate early termination of development, refusal of approval, or postmarketing drug withdrawal, there has been no empirical study on the completeness of intervention descriptions in registered DDI trials. Trialists and regulatory officials should devote more attention to the description of drug interventions when they are used concomitantly, as in DDIs.

What is the implication and what should change now?

- So far, trials on DDI, which are predominately in phase 1, have been mostly exempt from registration requirements. To avoid research waste, phase 1 trials should be included in registration legislation and intervention information required in both the registry and journal articles expanded and based on the TIDieR checklist focused on pharmacologic interventions in interventional trials.

[10]. Clinical research experts developed TIDieR to help authors better describe any intervention type within any study design [3,8]. In addition, reporting of particular data on interventions is a part of registration requirements under the Food and Drug Administration Amendments Act (FDAAA) [11] and the World Health Organization (WHO) Trial Registration Data Set (TRDS) [12].

Sufficient data for each intervention should be provided in the case of a combination of interventions [9,12], especially in clinical trials on drug−drug interactions (DDIs), where it is a prerequisite to enable the appropriate interpretation of DDIs [13−15]. Clinical DDI trials are specifically designed to detect DDI and inform regulatory decision-making on the benefits and risks of the investigational drug by comparing its effect in the absence and presence of concomitant medications [15]. The knowledge on potential DDIs should be acquired as soon as possible, mostly in phase 1 trials with healthy volunteers to ensure safety in subsequent phase two and three trials with patients, as well as after approval [14,15]. However, to our knowledge, the data on the completeness of descriptions of drug interventions in clinical trials on DDIs are lacking. Moreover, DDI trials registered in ClinicalTrials.gov were already shown to have suboptimal transparency regarding registration completeness [16], although DDIs are an important cause of drug-related adverse events and have led to several postmarketing withdrawals [17−22].

We assessed the adequacy of the reporting on drug-drug interventions in ClinicalTrials.gov and matching scientific publications for completed interventional trials investigating DDIs.

2. Methods

2.1. Dataset and inclusion criteria

For this observational study, a DDI was defined as a change in the effect of one drug, which could occur on pharmacodynamic or pharmacokinetic level, if another drug was previously or concomitantly administered [15,23]. A clinical trial in ClinicalTrials.gov was considered a trial on DDI if DDI was stated within the ClinicalTrials.gov Tabular View (1) in the study title or as the study objective or condition under the Descriptive Information section or (2) under the Tracking Information section as the outcome measure [16]. Completed studies were defined as "clinical studies that has ended normally, and participants are no longer being examined or treated [24]." Among 1,110 completed ClinicalTrials.gov trials on DDIs previously identified within a cohort of DDI trials registered until October 2015 [16], a total of 1,034 trials (93.2%) had a drug as the only intervention type. Considering that the median number of drug interventions recorded per trial was 2 (95% confidence interval 2.0−2.0; range 1−12) and the fact that the complexity of descriptions increases with the number of drugs included in the DDI trial, we restricted our analysis to trials that had (1) an interventional design and (2) a maximum of two drug interventions posted under the Intervention registration element of the Descriptive Information section in ClinicalTrials.gov (see Table A.1). A drug intervention was defined as any single substance or a fixed-dose combination of two active pharmaceutical ingredients, other than food and dietary supplements, which was intended for use in the diagnosis, mitigation, treatment, or prevention of disease [16,25] and which was recorded under the Intervention element in ClinicalTrials.gov and assigned to human participants to evaluate its interaction potential.

2.2. Identification of corresponding publications

The ClinicalTrials.gov trial search in October 2015 allowed at least 3 years for publishing trial results in a journal. Corresponding articles were identified in March 2019 by manually screening the Publications element under the ClinicalTrials.gov Tabular View and two electronic databases, PubMed/MEDLINE and Scopus, using the strategy adapted from the previously described [16]. We used (1)

National Clinical Trial number alone in SCOPUS or with the PubMed secondary source ID search tag [si] in PubMed (e.g., NCT00000419 [si]) [26]; (2) the drug's generic name, even for the drug code, if provided, but not reported in ClinicalTrials.gov; condition; study design characteristics and all names recorded in the Administrative Information section of ClinicalTrials.gov, as search terms combined using Boolean operators to yield any additional articles.

2.3. ClinicalTrials.gov data extraction

We assessed the completeness of registration data on pharmacological interventions in DDI trials using the 12-item TIDieR checklist, with instructions in Table A.2 as to how we interpreted each item for the purposes of this study. The data were extracted from the Descriptive Information section for all items except 10 and 12, which could be described only following the trial completion and were abstracted from the tab Study Results. We did not follow binary (yes/no) scoring from other studies using TIDieR items because they may decrease interrater reliability [27] but specified the differences in the registered and published data for individual TIDieR items. According to the definitions for the protocol registration data elements for interventional and observational studies in ClinicalTrials.gov [28], we hypothesized that most details on interventions would be posted under the Intervention element, including Intervention Type, Name(s) and Description, or under the Arm Description to differentiate each arm from other arms. Therefore, we collected data on registration elements within the Descriptive Information section (see Table A.1) in which any information on intervention was recorded, regardless of its clarity.

2.4. Publication data extraction

For trials with registered results, the following data were collected from the matching articles and online supplementary material: scientific journal, online publication date, publication title, and first author. Twelve TIDieR items (Table A.2) were extracted and compared with coded data abstracted from ClinicalTrials.gov. In cases of more published articles identified for a single trial, we reviewed intervention description only in the first published article.

2.5. Data analysis

Intervention data from ClinicalTrials.gov were reviewed for completeness independently by two investigators (D.J. and A.B.) from a 10% random sample of the cohort of trials to harmonize the extraction process. All four investigators confirmed the final extraction protocol (D.J., A.B., S.P., and A.M.), after which two investigators (D.J. and A.B.) carried out independent extraction of the full dataset from ClinicalTrials.gov and matching publications. We used a two-step strategy to assess information on interventions; initial scanning by keyword search terms and then detailed reading of the complete protocol within the Descriptive Information section and in published data. We performed descriptive analyses with data presented as frequencies using MedCalc version 17.9.4 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Characteristics in ClinicalTrials.gov of trials on DDIs with up to two drug interventions

Among 1,034 trials focused on DDIs from ClinicalTrials.gov that had a drug as the only intervention type registered under the Intervention element, we excluded 392 trials (37.9%), mostly because of listing ≥3 interventions or having an observational design (Fig. 1). For 642

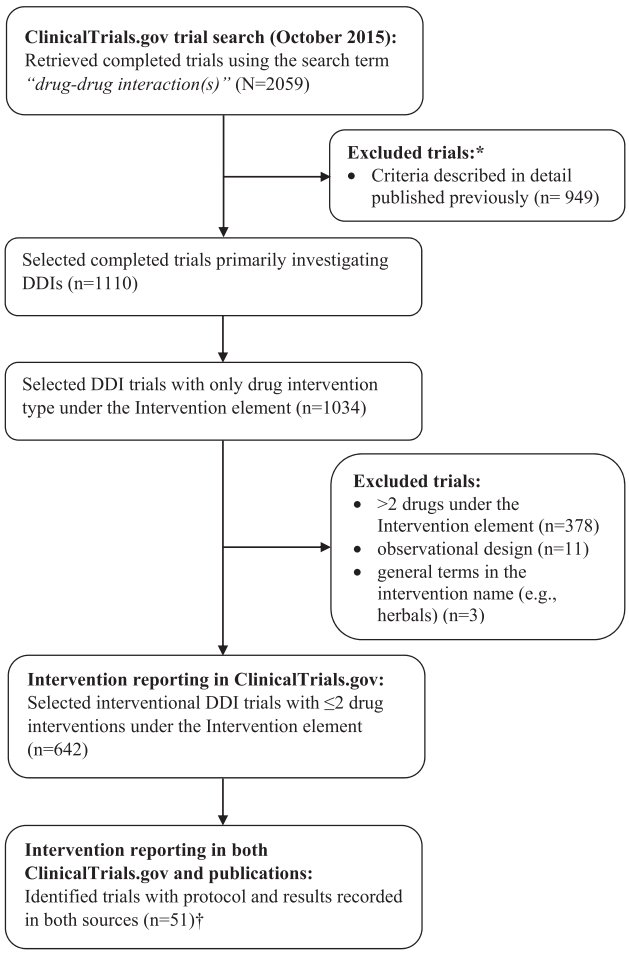

Fig. 1. Study flow diagram for the selection of eligible interventional trials on DDIs that had a maximum of two registered drug interventions in ClinicalTrials.gov. *Interaction of drug and ethanol, marijuana, MDMA, cocaine, nicotine (n = 67), food and juices (n = 29), dietary supplements (n = 11); interaction between two dietary supplements (n = 6); changed overall recruitment status (n = 2); or incorrectly identified words ''drug(s)'' or ''interaction(s)'' in registered data (n = 834). †A total of 52 trials had results reported both in ClinicalTrials.gov and journal articles, but the full text for one publication was unavailable (n = 51 trial in analysis).

Table 1. The description of the first six Template for Intervention Description and Replication (TIDieR) items within the Descriptive Information section for 1,180 drug interventions in 642 ClinicalTrials.gov trials on drug–drug interaction.

TIDieR item	Intervention description component	Number of interventions (*N* = 1,180), *n* (%)
TIDieR item 1	Generic name (INN)	
	Recorded	973 (82.5)
	Placebo	15 (1.3)
	Not recorded[a]	192 (16.3)
	Drug code name[b]	
	Recorded	332 (28.1)
	Placebo	15 (1.3)
	Not recorded	833 (70.6)
TIDieR item 2	Rationale, theory, or goal for intervention	
	Investigation of DDI stated only	24 (2.0)
	Clinical trial endpoints recorded only[c]	668 (56.6)
	Theoretical background or rationale provided	488 (41.4)
TIDieR item 3	Brand name	
	Recorded	334 (28.3)
	Placebo	15 (1.3)
	Not recorded[d]	831 (70.4)
	Manufacturer	
	Recorded	21 (1.8)
	Placebo	15 (1.3)
	Not recorded[e]	1,144 (96.9)
	Dosage form	
	Recorded clearly	453 (38.4)
	Unclear data or insufficient details[f]	11 (0.9)
	Not recorded	716 (60.7)
TIDieR item 4	Procedure	
	Recorded	191 (16.2)
	Not recorded	989 (83.8)
TIDieR item 5	Intervention provider	
	Explicitly stated[g]	4 (0.3)
	Not recorded	1,176 (99.7)
TIDieR item 6	Route of administration	
	Recorded clearly	673 (57.0)
	Only pharmaceutical dosage form recorded	150 (12.7)
	Route not recorded, data on dosage form inadequately described	6 (0.5)
	Not recorded	351 (29.7)

Abbreviations: DDI, drug–drug interaction; INN, International Nonproprietary Name.

[a] Only pharmacologic subgroup or class related to mechanism of action provided for three drugs (GK activator [$n = 2$] and anticonvulsant [$n = 1$], respectively).

[b] Specific combination of letters and numbers, such as GSK1349572, where letters can stand as abbreviation for pharmaceutical company (e.g., GlaxoSmithKline).

[c] Including pharmacokinetics, pharmacodynamics, safety, tolerability, or efficacy.

[d] Among these 831 interventions, 21.5% had only drug code name in the registry, 78.0% INN, alone or with code or manufacturer, 0.4% pharmacologic class, and 0.1% code with manufacturer.

[e] Among these 1,144 interventions, 15.6% had only drug code name in the registry, 83.3% INN, alone or with code or trade name, 0.8% only trade name or with code, and 0.3% pharmacologic class.

[f] Information such as solid dose forms (e.g., NCT01292993); 1T or 2T, probably denotes the number of tablets (e.g., NCT02387619); solution or suspension without any other details or data for route of administration (e.g., NCT02233244); or incongruent formulation under the Intervention Name and Intervention Description subelements (e.g., NCT00621101), respectively.

[g] Noted, but referring to general terms such as investigators ($n = 1$), care provider ($n = 2$), or clinical center staff ($n = 1$).

remaining trials, 1,180 pharmacological interventions were identified in the Intervention element and included in further analysis.

Interventional trials on DDIs were mostly without results reported in ClinicalTrials.gov; eight trials (1.2%) had results information submitted to ClinicalTrials.gov, but not yet publicly available, and 87 (13.6%; Table A.3) had results posted by March 2019. Most trials were in phase 1 (79.9%) and not covered by FDAAA requirements (88.5%; Table A.3). The pharmaceutical industry was the most common sponsor (74.1%).

3.2. The completeness of intervention descriptions in ClinicalTrials.gov

Only the code was used to describe 15.2% interventions (Table A.4). The international nonproprietary name (INN) was provided for most interventions (82.5%; Table 1), whereas manufacturer and brand names were poorly reported in ClinicalTrials.gov (1.8% and 28.3%, respectively). The intervention provider was the most frequently missing element (99.7%). For more than half of 1,180 registered interventions, data on dosage form were lacking within the Descriptive Information section (60.7%; Table 1).

Of 673 (57.0%) interventions for which route of administration was clearly noted, oral was the most common (88.1%). Neither dosage form nor route was recorded for 29.7% interventions (Table 2).

Doses used in trials were provided for most interventions (70.8%); however, a total of 198 interventions (16.8%; Table 3) did not have any information regarding dosing frequency. Planned strategies for adherence were recorded in ClinicalTrials.gov for only 10 interventions (0.8%; Table 3).

For almost one-fifth of interventions, any information related to the route of administration, dosing frequency, and treatment duration was not identified under the Intervention or Study Arms elements; instead, it was recorded under other data elements within the Descriptive Information section (18.4%, 20.0%, and 19.9%, respectively; Table A.5).

In 27 (4.2%) of 642 ClinicalTrials.gov trials on DDIs, the use of placebo was noted, most frequently under the Official Title (40.7%), but not within the Intervention element. A total of 139 trials (21.7%) did not have any information posted under the Intervention Description (ID) subelement; only the Intervention Name (IN) was recorded. Among 538 trials (83.8%) with 2 registered interventions, 54 trials (10.0%) listed both drugs under only one IN; 22 (4.1%) noted one drug under IN, and another under ID subelement; 294 (54.6%) posted an IN for each drug intervention, whereas the other 168 trials (31.2%) recorded more complex ≥2 IN subelements, mostly according to the study arms or treatment sequences.

Table 2. Data on pharmaceutical dosage form and route of administration recorded in ClinicalTrials.gov for 1,180 drug interventions in registered trials on drug–drug interaction

Dosage form and route reporting[a]	Number of interventions (*N* = 1,180), *n* (%)
Neither route of administration nor dosage form	351 (29.7)
Only route of administration	365 (30.9)
Only dosage form	150 (12.7)
Both route of administration and dosage form	303 (25.7)
Route of administration recorded, dosage form inadequately described	5 (0.4)
Route of administration not recorded, dosage form inadequately described	6 (0.5)

[a] Data were extracted from the ClinicalTrials.gov Descriptive Information section under the tab Tabular View.

3.3. Comparison of intervention descriptions in ClinicalTrials.gov and matching articles

Of 87 trials (13.6%) with results posted to ClinicalTrials.gov, 52 (59.8%) were published as well. Because the full text of one published trial was not available, we analyzed 51 trials with 96 drug interventions registered under the Intervention element. Among them, 60.8% were in phase 1, 27.4% in other phases (1/2, 2, 3, or 4), and 11.8% were without provided data.

We recorded both the drug code name and INN in the registry for 12 (12.5%) interventions, but only the INN was published for 10 (10.4%). The drug manufacturer was more frequently published in an article than recorded in the registry (45.8% vs. 5.2%; Table 4). The theoretical background or hypotheses underlying investigations of DDIs were published for 40.6% interventions with trial endpoints posted only in ClinicalTrials.gov. Procedures were described and congruent in both sources for 13.5% interventions, whereas the information on drug dosage form was not published for 43.8% interventions (Table 4). Among 39 interventions (40.6%) with registered and published information on dosage form, for 7 interventions (7.3%), data were assured solely under the References section of the article. The route by which the intervention was administered was more commonly recorded precisely in the article than in ClinicalTrials.gov (83.3% vs. 47.9%; Table 4). However, for eight interventions (8.3%), route was stated in the article only within assessed pharmacokinetic parameters (e.g., oral bioavailability).

Almost one-third of drug interventions did not have precisely provided and consistent information on intervention duration in both ClinicalTrials.gov and publications (30.2%; Table 5). Among them, four interventions (4.2%) had discordant number of total days of intervention administration in the article. Clear and matching data on dose and dosing frequency were identified in both sources for most interventions (87.5% and 61.5%; Table 5). However, only

Table 3. The description of the last six Template for Intervention Description and Replication (TIDieR) items within the Descriptive Information section and Study Results tab for 1,180 drug interventions in 642 ClinicalTrials.gov trials on drug–drug interaction

TIDieR item	Intervention description component	Number of interventions (*N* = 1,180), *n* (%)
TIDieR item 7	Location	
	Precisely described	143 (12.1)
	Only single or multicenter trial noted	157 (13.3)
	Only country, city, or nationality recorded[a]	32 (2.7)
	Country/nationality with single/multicenter trial	7 (0.6)
	No any data	841 (71.3)
TIDieR item 8	Dose	
	Recorded	835 (70.8)
	Placebo	15 (1.3)
	Not recorded[b]	330 (28.0)
	Dosing frequency	
	Recorded precisely	568 (48.1)
	Only total daily dose noted[c]	51 (4.3)
	Single dose as only used term	246 (20.8)
	Multiple or repeated dose alone or with single dose as used terms	106 (9.0)
	Unclear information[d]	11 (0.9)
	No any data[e]	198 (16.8)
	Duration of administration	
	Recorded clearly	774 (65.6)
	Single, multiple or repeated-dose administration, without clearly noted day(s) of administration	209 (17.7)
	Unclear information[f]	8 (0.7)
	No any data	189 (16.0)
TIDieR item 9	Tailoring	
	Recorded	93 (7.9)
	Not applicable	1,087 (92.1)
TIDieR item 10	Modifications	
	Different dose under Study Results[g]	2 (0.2)
	Not applicable	1,178 (99.8)
TIDieR item 11	Planned strategies for adherence	
	Recorded[h]	10 (0.8)
	Not recorded	1,170 (99.2)
TIDieR item 12	Results on participants' noncompletion	
	All participants completed	49 (4.2)
	Protocol deviation as only or among other reasons listed for withdrawal[i]	32 (2.7)
	Withdrawal because of other reasons or reasons not provided	85 (7.2)
	No any data[j]	1,014 (85.9)

[a] For a total of 1,059 (89.7%) interventions, location countries were listed under the Recruitment Information section of the ClinicalTrials.gov Tabular View.

[b] For 24 interventions (2.0%), the stable therapeutic dose was within the inclusion criteria or dosing requirements were specific, as for warfarin or heparin. Regarding all 330 interventions with absent dose, 48.8% had INN registered, 19.7% brand name, alone or with INN, code or both, 18.8% only code, 12.4% INN and code, and 0.3% only pharmacological subgroup.

[c] Only if terms such as "daily" or "per day" were along with the recorded dose.

[d] Mostly referring to unclear phrases such as total number of doses (e.g., NCT01112670) or tablets (e.g., NCT01525511) or incongruent dosing intervals for equal treatment period in different elements of the Descriptive Information section (e.g., NCT01080651), respectively.

[e] For 17 drug interventions (1.4%), stable administration was under the inclusion criteria or dosing requirements were specific.

[f] Information such as incongruent duration in different registration elements (e.g., NCT01991327) or recorded number of doses, which could imply number of days of administration (e.g., NCT01112670).

[g] Omeprazole 80 mg in the Descriptive Information (DI) vs. 40 mg in the results database (NCT01303445) and midazolam 6 mg in the DI section vs. 6 mg and 20 mg in the results database (NCT01989169).

[h] Telephone contact ($n = 2$), medication diary ($n = 4$), intervention container fitted with an electronic monitoring cap device ($n = 1$), witnessed administration ($n = 1$), and possibility to accommodate patients with scheduling conflicts ($n = 2$).

[i] Protocol violation mentioned in general or unwillingness to adhere to study requirement, missed drug dose, poor compliance, or noncompliance.

[j] Study results not provided or submitted, but not yet posted for 555 trials (86.4%) with 1,014 registered interventions.

Table 4. Comparison of the first six Template for Intervention Description and Replication (TIDieR) items for 96 interventions reported in ClinicalTrials.gov and published in 51 trials on drug–drug interaction[a]

TIDieR item	Intervention description in registry[b] vs. article	Number of interventions ($N = 96$), *n* (%)
TIDieR item 1	Generic name (INN)	
	Matching in ClinicalTrials.gov and article	87 (90.6)
	Registered single drug, published fixed-dose combination[c]	1 (1.0)
	Only in article	7 (7.3)
	Neither in ClinicalTrials.gov nor article	1 (1.0)
	Drug code name	
	Matching in ClinicalTrials.gov and article	9 (9.4)
	Only in ClinicalTrials.gov	11 (11.5)
	Only in article	1 (1.0)
	Neither in ClinicalTrials.gov nor article	75 (78.1)
TIDieR item 2	Rationale, theory, or goal for intervention	
	Theoretical background or rationale published	
	Only DDI investigation in ClinicalTrials.gov	4 (4.2)
	Clinical trial endpoints in ClinicalTrials.gov	39 (40.6)
	Theoretical background or rationale registered	53 (55.2)
TIDieR item 3	Brand name	
	Matching in ClinicalTrials.gov and article	20 (20.8)
	In both sources, but in article within reference[d]	13 (13.5)
	Only in ClinicalTrials.gov	13 (13.5)
	Only in article, provided clearly	13 (13.5)
	Only in article, but within reference[d,e]	8 (8.3)
	Neither in ClinicalTrials.gov nor article	29 (30.2)
	Manufacturer	
	Only in ClinicalTrials.gov	1 (1.0)
	In both sources, but in article within reference[d]	1 (1.0)
	In both sources, but in article different manufacturer within reference[d]	3 (3.1)
	Only in article, provided clearly	44 (45.8)
	Only in article, but within reference[d]	13 (13.5)
	Neither in ClinicalTrials.gov nor article	34 (35.4)
	Dosage form	
	Matching in ClinicalTrials.gov and article	31 (32.3)
	In both sources, but more general term published[f]	1 (1.0)
	In both sources, but in article within reference[d]	6 (6.3)
	In both sources, but in article different dosage form within reference[d,g]	1 (1.0)
	Only in ClinicalTrials.gov	18 (18.8)
	Only in article, provided clearly	14 (14.6)
	Only in article, but within reference[d]	1 (1.0)
	Neither in ClinicalTrials.gov nor article	24 (25.0)
TIDieR item 4	Procedure	
	Matching in ClinicalTrials.gov and article	13 (13.5)
	In both sources, but more detailed description published	10 (10.4)
	Only in ClinicalTrials.gov	12 (12.5)
	Only in article	42 (43.8)
	Neither in ClinicalTrials.gov nor article	19 (19.8)
TIDieR item 5	Intervention provider	
	Only in article[h]	7 (7.3)

(*Continued*)

Table 4. Continued

TIDieR item	Intervention description in registry[b] vs. article	Number of interventions ($N = 96$), n (%)
	Neither in ClinicalTrials.gov nor article	89 (92.7)
TIDieR item 6	Route of administration	
	Route recorded in ClinicalTrials.gov	
	Route published clearly	40 (41.7)
	Route indirectly stated in article[i]	4 (4.2)
	Neither route nor dosage form published	2 (2.1)
	Only dosage form in ClinicalTrials.gov	
	Route published clearly	22 (22.9)
	Route indirectly stated in article[i]	2 (2.1)
	Only dosage form published as well	2 (2.1)
	Neither route nor dosage form published	2 (2.1)
	Neither route nor dosage form in ClinicalTrials.gov	
	Route published clearly	18 (18.8)
	Route indirectly stated in article[i]	2 (2.1)
	Only dosage form published	2 (2.1)

Abbreviations: DDI, drug–drug interaction; INN, International Nonproprietary Name.

[a] A total of 52 trials had results reported both in ClinicalTrials.gov and journal articles, but the full text for one publication was unavailable ($n = 51$ trial in analysis).

[b] Data extracted from the ClinicalTrials.gov Descriptive Information section.

[c] Registered buprenorphine within the Descriptive Information section vs. published buprenorphine/naloxone (NCT00858962).

[d] Refers to the EMA's Summary of Product Characteristics (SmPC), or FDA documents entitled Package Insert or Prescribing Information (PI), Safety Information for Healthcare Professionals or FDA Briefing Document.

[e] For example, no brand name in the registry vs. FDA safety information for health care professionals and prescribing information for colchicine marketed as Colcrys under the References section (NCT00984061).

[f] "Syrup" as a term used in the registry vs. published phrase "oral liquid" (NCT00952653).

[g] Boceprevir tablets in ClinicalTrials.gov vs. Victrelis (boceprevir) capsule package insert under the References section (NCT01427504).

[h] Including terms as site personnel ($n = 4$), pharmacist ($n = 2$), or study nurse ($n = 1$).

[i] In publication used only phrases such as "total apparent oral clearance" or "oral bioavailability" (e.g., NCT01340196).

total daily dose or term "multiple-dose" were used in registration data for six interventions (6.3%), whereas distinct information on dosing frequency was published in the article. Descriptions did not specify planned strategies to improve participants' adherence neither in registered nor published data for 78.1% interventions. Only a single trial published a clear statement on adherence rate (Table 5).

4. Discussion

Our study of interventional trials on DDIs registered in ClinicalTrials.gov demonstrated that the prevalence of complete data reporting on drug interventions in the registry was low, with inconsistencies in relevant intervention data and discrepancies in the intervention description between ClinicalTrials.gov and matching journal publications.

To our knowledge, this is the first study to provide an overview of intervention descriptions in a public trial registry and published reports for registered trials on DDIs with pharmacologic intervention(s).

The following limitations should be addressed in interpreting the results. First, the external validity of our results could be affected by the use of a single registry; however, ClinicalTrials.gov is the largest public clinical trial database [29], holding almost 300,000 trial registrations in January 2019. Second, we did not analyze data for all trials on DDIs identified in our larger study ($n = 1{,}110$) [16]. We hypothesized that because the description of more than three drugs in a DDI study would be complex and the completeness of description of these interventions difficult to achieve, we concentrated on a more homogeneous sample based on a median of two interventions registered within the Intervention element in the whole DDI registration sample. In this way, we analyzed 57.8% of the total sample of DDI trials. Third, although we used a sensitive search strategy to reveal all published reports, there is still the possibility that we did not identify all publications. Finally, we did not assess the impact of reporting guidelines or registration requirements on trials registered or published in different years. It is possible that there have been improvements in reporting on drug intervention in recent years, which could not be detected in this study.

Contrary to the recommendations from the WHO TRDS [12], about one-third of drug interventions in our study had completely absent information on the investigated dose in the registry, whereas more than half lacked data on dosage

Table 5. Comparison of the last six Template for Intervention Description and Replication (TIDieR) items for 96 interventions reported in ClinicalTrials.gov and published in 51 trials on drug–drug interaction[a]

TIDieR item	Intervention description in registry[b] vs. article	Number of interventions ($N = 96$), n (%)
TIDieR item 7	Location	
	Described precisely in both sources	9 (9.4)
	Precisely in ClinicalTrials.gov, none or insufficient data[c] in article	14 (14.6)
	Precisely in article, none or insufficient data[c] in ClinicalTrials.gov	54 (56.3)
	None or insufficient data[c] in both sources	19 (19.8)
TIDieR item 8	Dose	
	Matching in ClinicalTrials.gov and article	84 (87.5)
	Different information published[d]	2 (2.1)
	Only in article[e]	10 (10.4)
	Dosing frequency	
	Recorded precisely in ClinicalTrials.gov	
	Matching in article	59 (61.5)
	Only total daily dose in ClinicalTrials.gov	
	Dosing frequency published clearly	2 (2.1)
	Single dose as only term in ClinicalTrials.gov	
	Equal term in article	21 (21.9)
	Multiple dose as only term in ClinicalTrials.gov	
	Dosing frequency published clearly	4 (4.2)
	Unclear data in ClinicalTrials.gov	
	Provided clearly in article	2 (2.1)
	Not recorded in ClinicalTrials.gov	
	Provided in article	7 (7.3)
	Only total daily dose published	1 (1.0)
	Duration of administration	
	Recorded in ClinicalTrials.gov	
	Matching in article	67 (69.8)
	Published interval within registered, but shorter[f]	2 (2.1)
	Different duration in article	2 (2.1)
	Unclear data in ClinicalTrials.gov	
	Provided clearly in article	2 (2.1)
	Not recorded in ClinicalTrials.gov[g]	
	Provided in article	23 (24.0)
TIDieR item 9	Tailoring	
	Matching in ClinicalTrials.gov and article	9 (9.4)
	Not applicable in both sources	87 (90.6)
TIDieR item 10	Modifications	
	Incongruent dose within CT.gov tabs, published dose as in Descriptive Information[h]	1 (1.0)
	Not applicable in both sources	95 (99.0)
TIDieR item 11	Planned strategies for adherence	
	Matching in ClinicalTrials.gov and article	2 (2.1)
	Only in ClinicalTrials.gov	1 (1.0)
	Only in article	18 (18.8)
	Neither in ClinicalTrials.gov nor article	75 (78.1)
TIDieR item 12	Adherence monitoring	
	All completed in ClinicalTrials.gov, adherence rate reported in article[i]	2 (2.1)

(*Continued*)

Table 5. Continued

TIDieR item	Intervention description in registry[b] vs. article	Number of interventions ($N = 96$), n (%)
	Matching PF report in both sources[j]	69 (71.9)
	Incomplete PF report in ClinicalTrials.gov or article	17 (17.7)
	Incongruent PF report	8 (8.3)

Abbreviations: CT.gov, ClinicalTrials.gov; PF, participant flow.

[a] A total of 52 trials had results reported both in ClinicalTrials.gov and journal articles, but the full text for one publication was unavailable ($n = 51$ in analysis).

[b] Data were extracted from the Descriptive Information section for all items except 10 and 12, which were abstracted from the tab Study Results.

[c] Data as single or multicenter trial, country, city or participants' nationality.

[d] Weight-based drug infusion doses in ClinicalTrials.gov vs. targeted plasma level and effect site level of interventions within the matching article.

[e] For two of 10 interventions without provided dose in the Descriptive Information section, stable therapeutic dose for at least several weeks or months was within the inclusion criteria under the Recruitment Information section.

[f] "A minimum of 4 days and up to 14 days" in the registry vs. published "6 or 7 days treatment" (NCT00858962).

[g] For a 15 of these 23 interventions (65.2%), single, multiple, or repeated-dose administration were without clearly noted day(s) of administration in the registry.

[h] Omeprazole 80 mg once daily (QD) under the Descriptive Information section, 40 mg QD within Study Results vs. 80 mg QD in the journal article (NCT01303445).

[i] Only one trial published a statement that all participants reported 100% adherence to the therapy (NCT01499498).

[j] Deviation from protocol requirements reported under withdrawal reasons for 11 (11.5%) interventions (protocol violation mentioned in general, missed drug dose, failure to take study drugs as outpatient, and noncompliance).

forms. The current version 1.3.1 of the WHO TRDS [12] includes Item 13, the IN and ID, which should be present for complete registration as required by the International Committee of Medical Journal Editors (ICMJE) for article submission [30]. The description of intervention components, such as "dose, duration, mode of administration," was already suggested in the first WHO dataset from 2006 (Version 1.1) [31,32]. The expanded FDAAA mandated the inclusion of the ID element to trial data, as specified in the 2016 Final Rule for Clinical Trials Registration and Results Information Submission, released by the NIH [33], and effective for trials initiated on or after January 18, 2017. This data element was formed to provide timely insight into the methodology of a trial and to possibly prevent biased results [33,34]. Nevertheless, we are mindful that 88% of analyzed trials were excluded from the FDAAA legislation and ICMJE requirements, mostly because of phase 1 status, which could be a potential source of bias in our study. Moreover, it should be kept in mind that information suggested for drug interventions in both FDAAA and WHO requirements includes passive or aspirational rather than compulsory language: "for example, interventions involving drugs may include dosage form, dosage, frequency and duration" [12,33].

Similar level of information as a requisite for the appropriate reporting on drug interventions is also a part of the 2010 CONSORT statement for clinical trial reports (Item 5) and 2013 SPIRIT statement for reporting trial protocols (Item 11), but these checklists require the route of administration noted and not the dosage form [10,35]. In our study, we showed that 12.7% of interventions recorded only the dosage form, whereas both the administration route and dosage form were clearly described only for one-fourth of analyzed interventions. To improve the quality of reporting on drug interventions even more, dosage form and route should be both distinctly covered by the regulatory requirements and reporting guidelines. Furthermore, although a drug's manufacturer is listed as one of the elements for adequate intervention descriptions in the 33-item SPIRIT checklist [10], this was accomplished in ClinicalTrials.gov for only 1.8% interventions in our study.

Along with the lack of important details describing the intervention in ClinicalTrials.gov for DDI trials, another issue of great concern is the finding of inconsistent data between the registered and published information. Less than a half of drug interventions in 51 trials with results reported in both sources clearly described and had matching data on dosage form, procedure, and route of administration in the two reports. The observed underreporting of components important for complete reporting of interventions is in line with the accumulating evidence of the poor quality of intervention descriptions in published journal articles [3–6,10,36]. Despite the fact that CONSORT guideline is widely adopted and shown to improve the quality of the reporting of randomized controlled trial (RCTs) [37], the reporting completeness remains suboptimal [38]. For example, in the analysis of descriptions of treatments from 51 RCTs reported in the *British Medical Journal*, one-third of drug interventions were not considered replicable [36]. Moreover, only 11% of oncology RCTs in phase 3 completely published all therapeutic details essential for application in clinical practice. Data on administration route were not ensured for 16% RCTs [6], which is less than 51% out of 642 registered trials that clearly provided the administration route for each intervention. Studies showed that drug interventions are better described in

comparison with nondrug interventions [3−5,36] and less challenging [39], but there are also studies that find no difference in the completeness of descriptions, such as in the *Health Technology Assessment* (*HTA*) journal (33.3% vs. 30.6% complete reports for drug and nondrug interventions, respectively; $P = 0.77$) [5]. All *HTA* reports on drug interventions from this study had information on the setting, and 73% noted the intervention provider [5], which is in contrast to our results, where we found remarkably lower rates in both the registry and the publications. However, we highlight that a comparative evaluation of studies investigating intervention description is limited because of the reporting of interventions different than drugs [27,39] or summarized reporting for both drug and nondrug treatments or use of different checklists with different levels of details provided for each assessed component [4−6,36].

Elements missing from the protocol can have important implications on patients' willingness to participate in trials, other researchers, external reviewers, and clinical practice [10,33]. The TIDieR checklist provides the widest and the most systematic instructions for describing a trial intervention and should be the cornerstone of providing usable evidence-based interventions. Considering differences in the description of drug and nondrug interventions, we recommend the development of distinct checklists and propose our interpretation of the TIDieR checklist as the starting point to improve the reporting of pharmacologic interventions in both trial registries and scientific journals. Regarding identified inconsistencies among registration elements that contained data on interventions, it behooves researchers to describe each drug intervention in detail within the ID subelement when submitting their protocol data. Furthermore, to promote reporting, ClinicalTrials.gov administrators should increase the current 1,000-character limit for this subelement [28] as well. Lacking important details in the description of drug interventions in the registry and matching publications demonstrate that there is insufficient quality control of data by data providers, ClinicalTrials.gov administrators, and journal editors, emphasizing much-needed enforcement of complete descriptions of drug interventions.

5. Conclusion

Despite the expectation that the descriptions of drug interventions would be less complex than of nonpharmacologic interventions, the reporting of interventions identified in trials on DDIs registered in ClinicalTrials.gov and published in journal articles was inadequate. Potential solutions to elevate reporting on pharmacologic interventions include regulatory reforms, specifically for phase 1 trials, more stringent requirements, and broader instructions based on the TIDieR checklist for all components related to drug interventions that have to be posted or published and the assessment of the completeness of intervention data during the registration and publication process.

CRediT authorship contribution statement

Diana Jurić: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Adriana Bolić:** Methodology, Formal analysis, Investigation, Writing - review & editing. **Shelly Pranić:** Methodology, Writing - review & editing, Visualization. **Ana Marušić:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Acknowledgments

Not applicable.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.10.002.

References

[1] Goldacre B, DeVito NJ, Heneghan C, Irving F, Bacon S, Fleminger J, et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. BMJ 2018;362:k3218.
[2] Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405−8.
[3] Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.
[4] Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? BMJ 2008;336:1472−4.
[5] Douet L, Milne R, Anstee S, Habens F, Young A, Wright D. The completeness of intervention descriptions in published National Institute of Health Research HTA-funded trials: a cross-sectional study. BMJ Open 2014;4(1):e003713.
[6] Duff JM, Leather H, Walden EO, LaPlant KD, George TJ Jr. Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application. J Natl Cancer Inst 2010;102:702−5.
[7] Hariohm K, Jeyanthi S, Kumar JS, Prakash V. Description of interventions is under-reported in physical therapy clinical trials. Braz J Phys Ther 2017;21(4):281−6.
[8] Alvarez G, Cerritelli F, Urrutia G. Using the template for intervention description and replication (TIDieR) as a tool for improving the design and reporting of manual therapy interventions. Man Ther 2016;24:85−9.
[9] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
[10] Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.
[11] Food and Drug Administration Amendments Act of 2007. 21 U.S.C. Public Law 110-85 2007: Sect. 801. Available at http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf. Accessed May 15, 2019.

[12] World Health Organization. WHO Data Set. Geneva, Switzerland: World Health Organization. Available at http://www.who.int/ictrp/network/trds/en/. Accessed May 15, 2019.
[13] Ministry of Health, Labour and Welfare Research Group. Drug interaction guideline for drug development and labeling recommendations. Tokyo: Ministry of Health, Labour and Welfare; 2014. Available at https://www.solvobiotech.com/documents/Japanese_DDI_guideline_(draft)_2014Jan.pdf. Accessed May 15, 2019.
[14] European Medicines Agency. Guideline on the investigation of drug interactions. London: European Medicines Agency; 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf. Accessed May 15, 2019.
[15] US Food and Drug Administration. Clinical drug interaction studies—study design, data analysis, and clinical implications. Silver Spring, MD: US Food and Drug Administration; 2017. Available at https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf. Accessed May 15, 2019.
[16] Jurić D, Pranić S, Tokalić R, Milat AM, Mudnić I, Pavličević I, et al. Clinical trials on drug-drug interactions registered in ClinicalTrials.gov reported incongruent safety data in published articles: an observational study. J Clin Epidemiol 2018;104:35−45.
[17] Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab Dispos 2003;31:815−32.
[18] World Health Organization. Pharmaceuticals: restrictions in use and availability. Geneva, Switzerland: World Health Organization; 2001. Available at http://apps.who.int/medicinedocs/en/d/Js2203e/2.6.html#Js2203e.2.6. Accessed May 15, 2019.
[19] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med 2001;2(5):205−7.
[20] Gottlieb S. Antihistamine drug withdrawn by manufacturer. BMJ 1999;319:7.
[21] Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264:2788−90.
[22] SoRelle R. Withdrawal of Posicor from market. Circulation 1998;98:831−2.
[23] Cascorbi I. Drug interactions—principles, examples and clinical consequences. Dtsch Arztebl Int 2012;109(33−34):546−55. quiz 556.
[24] US National Library of Medicine. Glossary of common site terms. Bethesda, MD: US National Library of Medicine; 2019. Available at https://clinicaltrials.gov/ct2/about-studies/glossary. Accessed August 12, 2019.
[25] US Food and Drug Administration. Drugs@FDA Glossary of Terms. Silver Spring, MD: US Food and Drug Administration; 2017. Available at https://www.fda.gov/drugs/informationondrugs/ucm079436.htm. Accessed August 12, 2019.
[26] US National Library of Medicine. Clinical trial registry numbers in MEDLINE/PubMed records. Bethesda, MD: US National Library of Medicine; 2019. Available at https://www.nlm.nih.gov/bsd/policy/clin_trials.html. Accessed May 15, 2019.
[27] Liljeberg E, Andersson A, Lovestam E, Nydahl M. Incomplete descriptions of oral nutritional supplement interventions in reports of randomised controlled trials. Clin Nutr 2018;37(1):61−71.
[28] US National Library of Medicine. ClinicalTrials.gov protocol registration data element definitions for interventional and observational studies. Bethesda, MD: US National Library of Medicine; 2019. Available at https://prsinfo.clinicaltrials.gov/definitions.html. Accessed May 15, 2019.
[29] Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 years after the ICMJE policy was established. N Engl J Med 2017;376:383−91.
[30] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Lancet 2004;364:911−2.
[31] Moja LP, Moschetti I, Nurbhai M, Compagnoni A, Liberati A, Grimshaw JM, et al. Compliance of clinical trial registries with the World Health Organization minimum data set: a survey. Trials 2009;10:56.
[32] World Health Organization. International Clinical Trials Registry Platform (ICTRP): WHO Trial Registration Data Set Archive. Geneva, Switzerland: World Health Organization; 2019. Available at https://www.who.int/ictrp/network/trds_archive/en/. Accessed May 15, 2019.
[33] Final Rule: clinical trials registration and results information submission. Fed Regist 2016;81:64981−5157.
[34] Fairman KA, Curtiss FR. What should be done about bias and misconduct in clinical trials? J Manag Care Pharm 2009;15(2):154−60.
[35] CONSORT Group. The CONSORT 2010 statement. CONSORT Group. 2010. Available at http://www.consort-statement.org/checklists/view/32–consort-2010/78-interventions. Accessed May 15, 2019.
[36] Schroter S, Glasziou P, Heneghan C. Quality of descriptions of treatments: a review of published randomised controlled trials. BMJ Open 2012;2(6). https://doi.org/10.1136/bmjopen-2012-001978.
[37] Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust 2006;185:263−7.
[38] Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Syst Rev 2012;1:60.
[39] Candy B, Vickerstaff V, Jones L, King M. Description of complex interventions: analysis of changes in reporting in randomised trials since 2002. Trials 2018;19(1):110.