

# Therapeutic drug monitoring (TDM) as intervention: A cross-sectional analysis of characteristics of 173 registered clinical trials

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## ARTICLE INFO

### Keywords:

WHO International clinical trials registry  
Clinical trials  
Therapeutic drug monitoring  
TDM

## ABSTRACT

**Background:** To examine fundamental characteristics of clinical trials with therapeutic drug monitoring (TDM) as intervention on world major clinical trials registry platform.

**Methods:** Cross-sectional analysis of clinical trials with TDM as intervention that were registered on WHO International Clinical Trials Registry Platform (ICTRP) or [ClinicalTrials.gov](http://ClinicalTrials.gov). Relevant trial entries registered before and on March 2nd, 2022 were downloaded, deduplicated, and reviewed. Recruit country, monetary source, start years, study design, medical conditions, involved drugs, outcome measure, and subject information were extracted and analyzed.

**Results:** Overall, 173 clinical trials were included in this study. Majority of the trials were conducted in several economically prosperous countries. The earliest initiated trials dates back to 2002. Most of the trials were funded by hospitals (36.4%). A higher proportion of trials were conducted within one country (86.1%), as phase IV (34.1%) interventional study (82.7%), randomized (52.6%), parallel assignment (53.8%) and open label (67.0%). The most concerned medical condition were infectious or parasitic disease and neoplasms, with the most monitored drugs were immunosuppressants and  $\beta$ -lactam antibacterials. Most of the trials enroll no more than 50 subjects (30.6%), with both gender (95.4%), and adults (67.0%).

**Conclusion:** The trials were mainly conducted in several economically prosperous countries. The number of registered trials had gradually increased during the past years. Novel biological drugs have increasingly become the research hotspot. We expect that with abundant financial support, more high-quality large-scale, multicenter randomized clinical trials (RCTs) are designed and implemented to promote the development of TDM in the future.

## 1. Introduction

For some drugs, patients manifest great discrepancies in response to their intervention, thus this kind of drugs therapy should not be a one-size-fits-all approach. Therapeutic drug monitoring (TDM) refers to the measurement and adjustment of drug concentration within the body in order to maximize the drug efficacy and minimize the toxicity. Therefore, the incorporation of TDM in clinical practice can enable healthcare professionals to optimize drug treatment. Conventional TDM was started way back in the 1960s [1]. Over the past several decades, TDM has made a substantial contribution to personalize pharmacotherapy [2]. In the current times, the scope of TDM has extended to be applied in various medical conditions. As useful practical tool, there are many clinical trials about TDM worldwide. Since 2005, the International

Committee of Medical Journal Editors (ICMJE) required that the registration of clinical trials is the prerequisite of publication as papers [3,4]. There are several recognized publicly-accessible clinical trial registry platforms worldwide, responsible party of clinical trials like sponsors or investigators submit trials' information to the web-based system. The registered clinical trials with TDM as intervention are greatly heterogeneous in terms of location, sponsor, monitored drugs and design, however, the general overview of these trials was limited.

In this article, we aimed to assess the characteristics of all the registered clinical trials with TDM as intervention, summarize the basic information about these trials like how many registered trials are there globally, who provide monetary support to the trials, and what kinds of drugs are monitored etc. The results of this study can help to better review current scientific practice in the field of TDM, help researchers

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<https://doi.org/10.1016/j.conctc.2022.101014>

Received 8 June 2022; Received in revised form 30 August 2022; Accepted 1 October 2022

Available online 12 October 2022

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**Table 1**

List of clinical trial registry platforms assessed in this study.

Country or region	Organization	Uniform resource locator (URL)
Australia and New Zealand	Australian New Zealand Clinical Trials Registry (ANZCTR)	<a href="http://www.anzctr.org.au/">http://www.anzctr.org.au/</a>
Brazil	Brazilian Clinical Trials Registry (ReBec)	<a href="http://www.ensaio.sclnicos.gov.br/">http://www.ensaio.sclnicos.gov.br/</a>
China	Chinese Clinical Trial Registry (ChiCTR)	<a href="http://www.chictr.org/en/">http://www.chictr.org/en/</a>
South Korea	Clinical Research Information Service (CRIS), Republic of Korea	<a href="https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp">https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp</a>
India	Clinical Trials Registry - India (CTRI)	<a href="http://ctri.nic.in/Clinicaltrials/login.php">http://ctri.nic.in/Clinicaltrials/login.php</a>
Cuba	Cuban Public Registry of Clinical Trials (RPCEC)	<a href="http://registroclinico.sld.cu/">http://registroclinico.sld.cu/</a>
European Union	EU Clinical Trials Register (EU-CTR)	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>
Germany	German Clinical Trials Register (DRKS)	<a href="https://drks-neu.uniklinik-freiburg.de/drks_web/">https://drks-neu.uniklinik-freiburg.de/drks_web/</a>
Iran	Iranian Registry of Clinical Trials (IRCT)	<a href="http://www.irct.ir/">http://www.irct.ir/</a>
United Kingdom	International Standard Randomized Controlled Trial Number Register (ISRCTN)	<a href="http://www.isrctn.org/">http://www.isrctn.org/</a>
Japan	Japan Registry of Clinical Trials (JRCT)	<a href="http://rctportal.niph.go.jp/">http://rctportal.niph.go.jp/</a>
Lebanon	Lebanese Clinical Trials Registry (LBCTR)	<a href="https://lbctr.moph.gov.lb/">https://lbctr.moph.gov.lb/</a>
Thailand	Thai Clinical Trials Registry (TCTR)	<a href="https://www.thaiclinicaltrials.org/">https://www.thaiclinicaltrials.org/</a>
Netherlands	The Netherlands National Trial Register (NTR)	<a href="http://www.trialregister.nl/trialreg/index.asp">http://www.trialregister.nl/trialreg/index.asp</a>
Pan Africa	Pan African Clinical Trial Registry (PACTR)	<a href="http://www.pactr.org/">http://www.pactr.org/</a>
Peru	Peruvian Clinical Trial Registry (REPEC)	<a href="https://ensayosclnicos-repec.ins.gob.pe/en/">https://ensayosclnicos-repec.ins.gob.pe/en/</a>
Sri Lanka	Sri Lanka Clinical Trials Registry (SLCTR)	<a href="http://www.slctr.lk/">http://www.slctr.lk/</a>
United States	ClinicalTrials.gov	<a href="http://www.clinicaltrials.gov/">http://www.clinicaltrials.gov/</a>

avoid repeated trials and identify gaps in scientific work.

## 2. Methods

### 2.1. Data source and search strategy

This study just uses public-accessible data to do the analysis, thus do not need ethics committee approval.

WHO International Clinical Trials Registry Platform (ICTRP) and [ClinicalTrials.gov](http://ClinicalTrials.gov) are the globally major clinical trial registry platform. As listed in [Table 1](#), registries from 17 countries or religions composed the WHO ICTRP primary registry network. The 17 countries or religions include Australia and New Zealand, Brazil, China, South Korea, India, Cuba (the website cannot be visited for unknown reason), European Union, Germany, Iran, United Kingdom, Japan, Lebanon, Thailand, Netherlands, Pan Africa, Peru, and Sri Lanka. Each participating country sends their data to ICTRP. [ClinicalTrials.gov](http://ClinicalTrials.gov) is a registry of clinical trials conducted in 220 countries maintained by the United States National Library of Medicine on behalf of the National Institutes of Health (NIH). The WHO ICTRP and [ClinicalTrials.gov](http://ClinicalTrials.gov) require the trial registration to meet the specific standards in terms of unique identification, required content, optional content, validity and the requirements of ICMJE.

All of the platforms permit public access to its records, and all of them offer English version websites. Some platforms provide advanced search or extended search function, and there is “intervention” filter included. These platforms include ANZCTR, ChiCTR, CRIS, CTRI, IRCT, ISRCTN, LBCTR, TCTR, PACTR and [ClinicalTrials.gov](http://ClinicalTrials.gov). Some platforms only have simple search or basic search function, like ReBec, NTR,

REPEC, and SLCTR. These platforms have no more filter choices. For EU-CTR and DRKS, their advanced search function does not include “intervention” filter. For JRCT, there is only one search function, but “intervention” filter was included. To identify clinical trials with TDM as intervention registered in these platforms, we put keywords “therapeutic drug monitoring” or abbreviation ‘TDM’ in the “intervention” filter to precisely narrow down the search results, or put keywords in the title or default search box if without “intervention” filter.

It is worth noting that a clinical trial is not limited to be registered in only one platform, so one clinical trial may have different identity code (ID) in various platforms. Some of the platforms provide ID of the clinical trials both in this platform and other platforms, for example, ISRCTN provides not only ISRCTN ID, but also additional identifier including EU-CTR number and [ClinicalTrials.gov](http://ClinicalTrials.gov) number. If a clinical trial was registered on more than one platform, it will only be recorded as one trial. In addition, titles of the trials were compared to find the duplicated trials further.

After these searches and the duplicated trials removed, we reviewed the title and abstract of the remaining registry records to assess eligibility. The inclusion criteria were: (1) TDM is one of the intervention means. (2) Use of drugs or biologics for prophylaxis, diagnosis and treatment. (3) Be available on the registry platforms on March 2nd, 2022. The exclusion criteria were: (1) Without summary on the registry platform. (2) Medical device clinical trial. (3) Unrelated to TDM, for example, T-DM1 means trastuzumab emtansine, or TDM is the abbreviation of treatment decision maker. Two reviewers (Chang and Zhang) independently reviewed the screened records in detail. Any disagreement was resolved by a third reviewer (Zhao).

### 2.2. Data extraction and analysis

In helping users find trials, the internationally available platform websites offer general information about the trials: title, participating sites, sponsor name, principal investigator, start and end time, study design, outcome measures, patient selection criteria, enrollment goal, date posted, and other pertinent data. The records from the platforms database could be downloaded as TXT, PDF or XML datasets. We extracted the following information from each included trial: registry platform, ID, scientific title, public title, recruitment country, monetary source, starting date, study design including study type, phase (0, 1, 2, 3, 4, and trials that do not have an Food and Drug Administration (FDA)-defined phase), allocation (randomized or non-randomized), intervention model, and masking (open or blinded), medical condition, monitored drugs, outcome measure, subject information including sample size, subject gender, and subject minimum age. In most cases, the needed information is listed under the existing field names. Sometimes the information is derived from multiple data elements and is not available as a discrete field in the platform database.

If a trial recruit subjects in more than one country, the trial will be considered as international multi-center trial, and the location of the trial will be recorded once for each participating country. Monetary source is who provide the monetary support to the trial, or funder type. We used the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) to itemize medical conditions into major therapeutic categories. Outcome measures of all trials were classified as drug level, biomarker, clinical outcomes, clinical scale, adverse events, cost, and acceptability. Drug level is the drug concentration in the body. Biomarker includes any blood test. Clinical outcomes include symptoms, clinical remission, progression-free-survival (PFS), hospitalization or death etc.; clinical scales include like body mass index z-scores, quality of life (KDQoL-SF). Acceptability is patients’ perspective towards TDM. Sample size is the planned or actual number of participants to be enrolled. We didn’t record recruitment status for the progress of the registered clinical trials on the platforms are not updated in time. If the content under the targeted data elements is missing, or cannot be inferred from the abstract, we record it as “Not

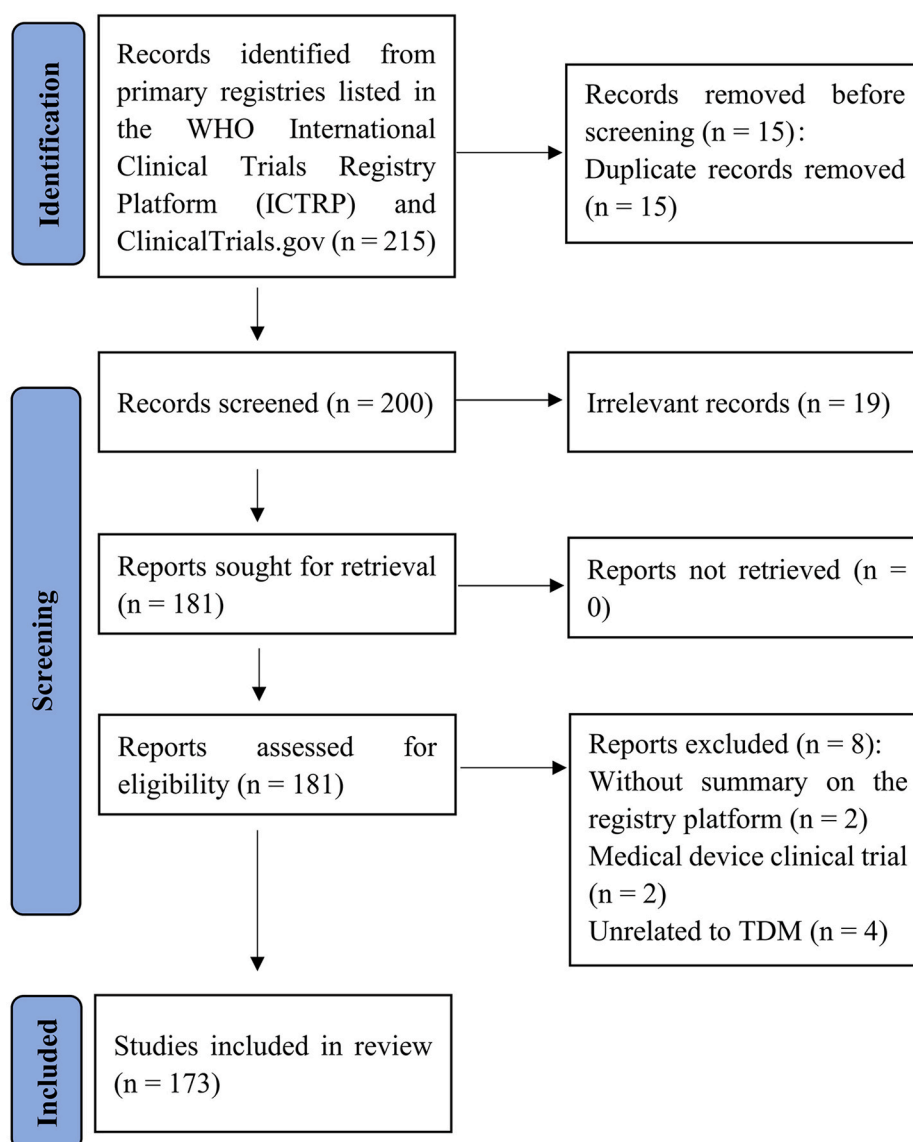


Fig. 1. PRISMA flow diagram.

reported”.

We used descriptive statistics to analyze the extracted data. We summarized the characteristics of all included trials using frequency and percentages. We used SAS 9.4 (SAS Institute) and Excel 2016 (Microsoft Corporation) for all analyses.

### 3. Results

#### 3.1. Eligible clinical trials

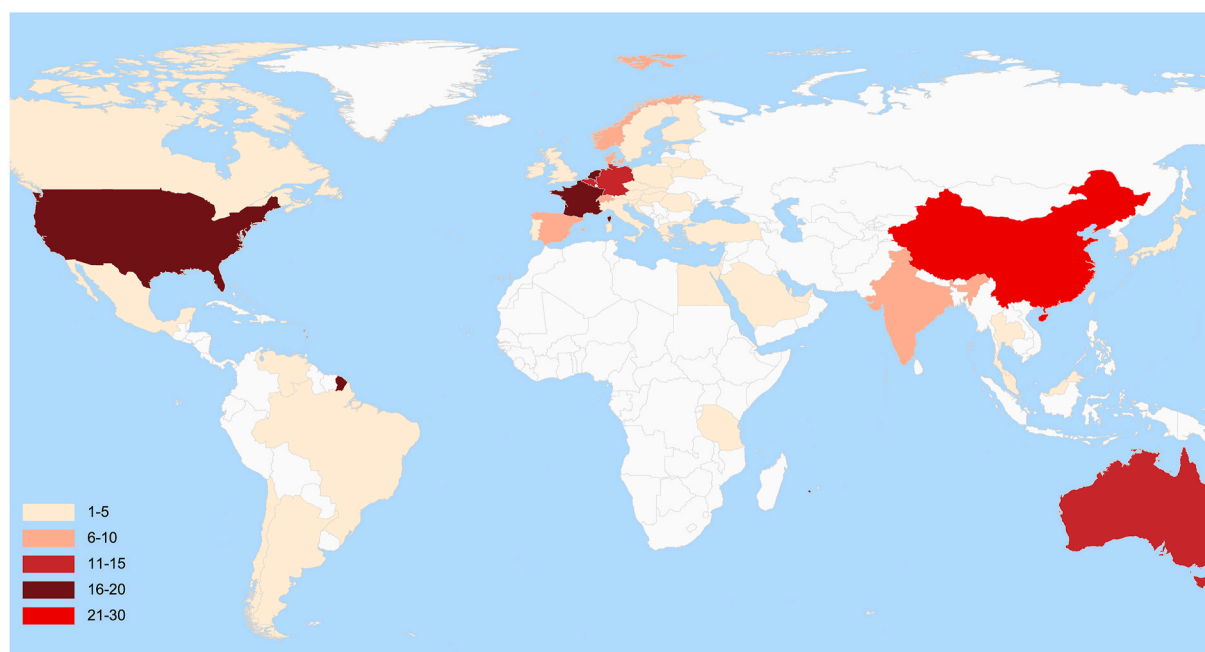
We screened all the trials from inception to March 2nd, 2022, in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart (Fig. 1). At first a total of 215 records were retrieved. After the duplicated and irrelevant removed, we entered 173 records (ANZCTR: 11, ChiCTR: 19, CRI: 1, CTRI: 6, EU-CTR: 20, DRKS: 2, ISRCTN: 3, JRCT: 2, NTR: 13, ClinicalTrials.gov: 96) into this study. ReBec, PRCEC, IRCT, LBCTR, TCTR, PACTR, REPEC, SLCTR contributed no eligible records to this study.

#### 3.2. Characteristics of included clinical trials

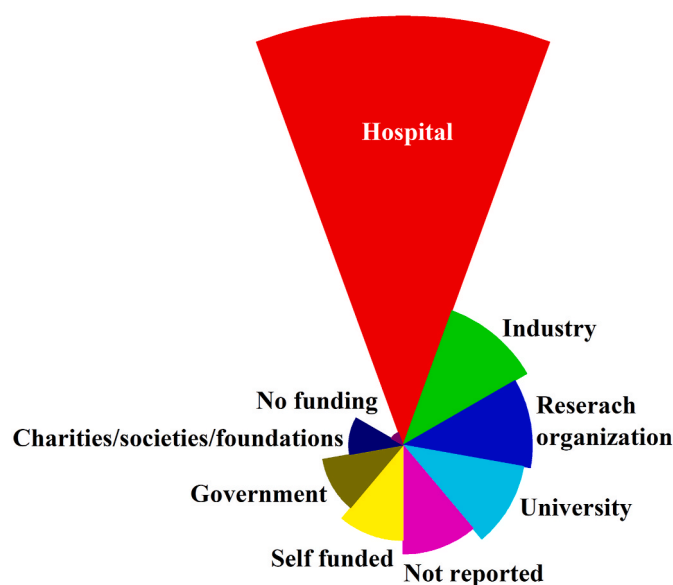
##### 3.2.1. General information

Among the 173 trials, 149 trials (86.1%) were single center trials or domestic multi-center trials, 11 trials (6.4%) were international multi-center trials. We marked the numbers of trials of various countries on the world map for clear presentation in Fig. 2. For trials conducted in multiple sites in different countries, each country was counted once. There are 28 trials (16.2%) conducted in China, which ranked number one in the world. West Europe, United States and Australia followed China. Large part of Africa and north and west Asia are blank, meaning there are no eligible trials included from these regions.

Most of the included clinical trials were funded by hospitals (36.4%), then followed by pharmaceutical company (12.1%), or industry. Research organization and university ranked the third and fourth respectively (10.98% and 10.4%). Fourteen trials (8.1%) were supported by the principal investigator's own money. Government funds (6.9%) come from government like Shanghai government public funds. Charities/Societies/Foundations (4.6%) refer to non-commercial bodies like Chinese Pharmaceutical Association. Two trials (1.2%) have no funds, and one of them stated that patients pay for their own expense (ChiCTR2200055499). One trial listed its monetary source as “special



**Fig. 2.** Locations of included clinical trials, the color block in the lower left corner represents the number of trials. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 3.** Funder type of included clinical trials.

funds" but did not clarify what was special funds (ChiCTR2000036845). For these trials, their funder type was classified as not reported (9.2%). The results are shown in Fig. 3.

From Fig. 4 we can see that the earliest initiated registered clinical trials dates back to 2002. The first started two trials were NCT00032669 and NCT00122590. But NCT00122590 was first posted in 2005 on the website. Since 2002, the numbers of trials have an upward trend. The climax is in 2020 with 23 trials.

### 3.2.2. Study design

Design characteristics of included trials are given in Fig. 5. Most trials were interventional study (82.7%), phase IV (34.1%), parallel assignment (53.8%), randomized (52.6%), and open (67.0%).

The study type of 26 trials (15.0%) were not mentioned, 2.31% of the

trials are observational study. Phase 0 to phase III categories were applied to 2 (1.2%), 8 (4.6%), 18 (10.4%), and 18 (10.4%) clinical trials respectively. Forty-five trials (26.0%) were registered as study phase not applicable to them. For intervention model, single group assignment (26.6%), non-parallel assignment (7.5%), crossover assignment (1.7%), sequential assignment (1.7%), case-control study (1.2%), before-and-after study (0.6%), factorial assignment (0.6%), not reported (6.4%). Twenty-nine trials indicated that they were non-randomized (16.8%). The masking of 21 trials were not mentioned (12.1%), the rest blinded trials are (single blind: 9.2%, double blind: 5.2%, triple blind: 1.7%, quadruple blind: 2.3%, not detailed: 2.3%).

### 3.2.3. Medical condition, monitored drugs and outcome measure

Fig. 6 revealed the ICD-10 categories of medical condition of included clinical trials. Infectious or parasitic disease is the most concerned targeted disease (35.0%), then comes neoplasms (13.3%). Digestive disease ranked third (12.8%). One trial only recruited healthy subject (NCT01777685). The top 10 most monitored drugs are vancomycin, adalimumab, tacrolimus, voriconazole, lopinavir, ritonavir, efavirenz, methotrexate, piperacillin/tazobactam, tocilizumab. Involved drugs were classified into categories according to WHO Anatomical Therapeutic Chemical (ATC) Classification [5] in Table 2. There are 11 kinds of drugs under selective immunosuppressants category with totally 27 trials: abatacept, baricitinib, cyclosporine, eculizumab, sirolimus, tacrolimus, tofacitinib, upadacitinib, vedolizumab, mycophenolate mofetil, and leflunomide. Adalimumab, certolizumab, etanercept, golimumab, and infliximab were under tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors category with 23 trials. Beta-lactam antibacterials category contains amoxicillin, benzylpenicillin, imipenem/cilastatin, meropenem, piperacillin/tazobactam, cefazolin, cefotaxime, ceftriaxone and 4 kinds of unknown drugs with 21 trials in total. We have comprehensively outlined and summarized the primary and secondary outcome measure of the eligible trials, and the results are shown in Fig. 7. Drug level (47.4%) is the mostly used trial endpoint, clinical outcome (37.0%) and adverse events (28.3%) come afterwards. There are 9.6% and 7.5% of trials used biomarker and clinical scale respectively. Six-point-forty-three percent of the trials studied cost, and 0.7% of the trials concerned with acceptability. Seventeen trials (9.8%)



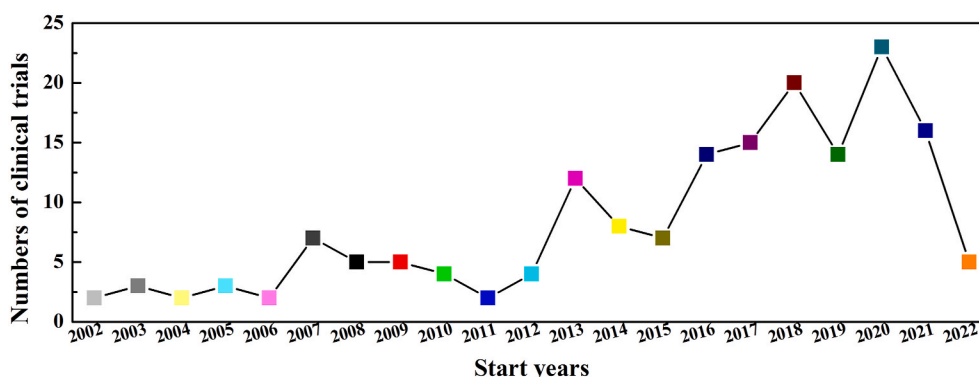


Fig. 4. Start years of included clinical trials.

just mentioned they use efficacy as outcome measure, but not specified what endpoint it was. One clinical trial mentioned that the biological samples collected for drug concentration was saliva (NCT04124055), another one was hair (NCT03691961). Although the numerous clinical trial registry platform database contains many data elements or fields, the only one with a results database is [ClinicalTrials.gov](https://clinicaltrials.gov) [6]. In our study, there are only 6 out of 96 trials in [ClinicalTrials.gov](https://clinicaltrials.gov) reported results.

#### 3.2.4. Subject information

Fig. 8 revealed that 53 trials (30.6%) recruited or plans to recruit less than or equal to 50 subjects. The sample size of 38 trials (22.0%) was between 51 and 100, similarly, 38 trials' sample size was between 101 and 200. The number of subjects of NL7354 was not reported. Three trials (1.7%) only recruit female subjects, and 5 trials (2.9%) only recruit male subjects. Except missing value from 10 trials (5.8%), the rest trials (89.6%) recruit both gender subjects. Majority of the trials (67.0%) recruit subjects over 18 years old, which is considered to be adults in most parts of the world. Clinical trials recruiting newborns, infants, children, adolescents, as well as old adults also exist. Several trials related to anti-infective agents explicitly mentioned they were done on critically ill patients (ICU patients): NCT03990467, NCT01965340, NCT01185405, 2018-003496-36, and NL7018.

## 4. Discussion

WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov) are online resources for health care professionals, researchers, patients, and the general public. It should be noted that there is no charge for trials registration. Although WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov) provides a portal to registered clinical trials worldwide, all the registry platforms are independent and at the same time, have duplicated registered records between platforms. Since there are no unified and integrated global clinical trials platform, no global clinical trials database can provide a unique list of clinical trials for electronic download, which makes it difficult for aggregate analysis. In this study, we delicately screened the 18 registry platforms one by one, and composed a dataset without duplicate records, but with all the data elements needed.

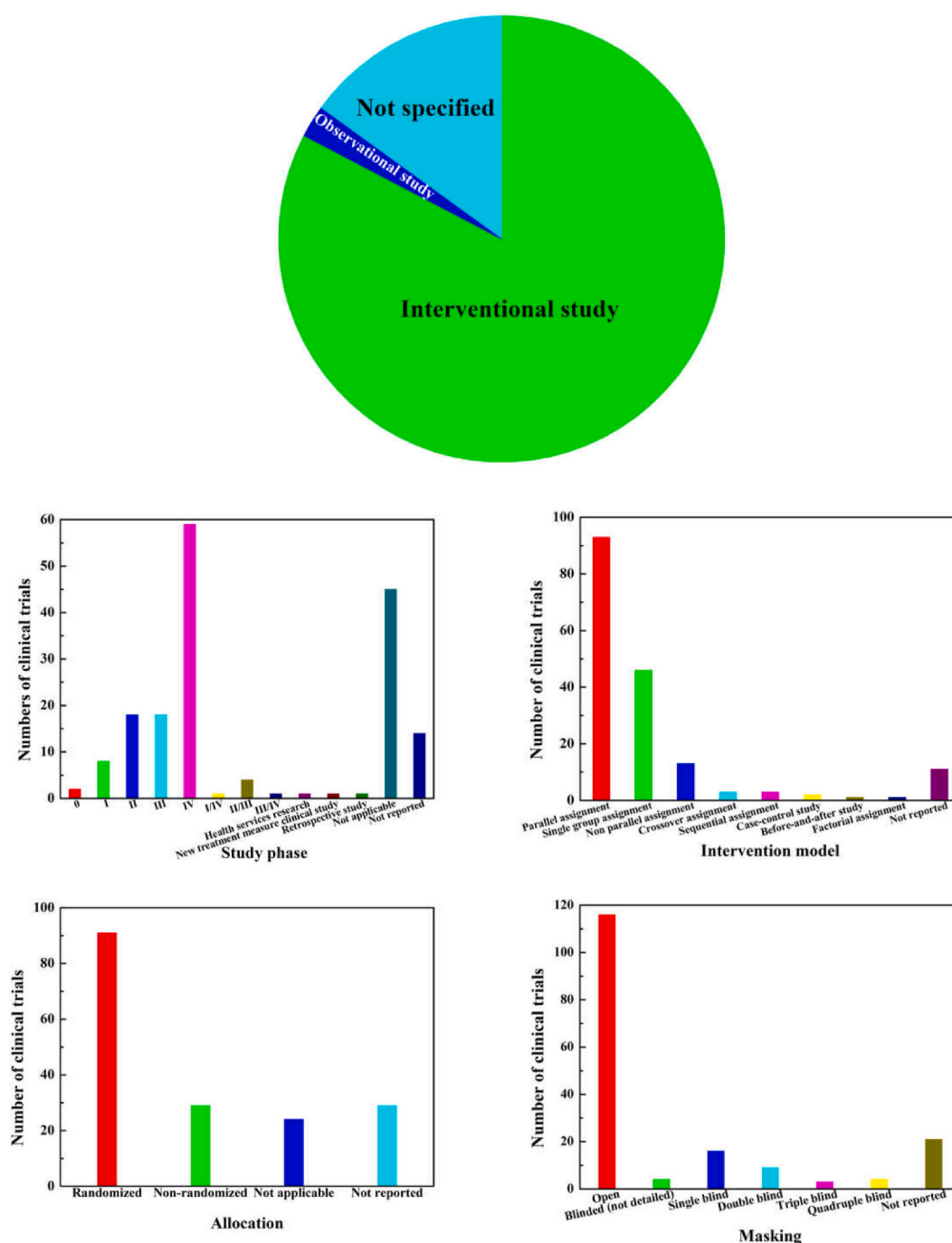
Analyzing clinical trials metadata can illuminate the characteristics of the trials, such as the type, size and design. In this study, we comprehensively analyzed and generalized the general information, study design, medical condition, monitored drugs and outcome measure as well as subject information of clinical trials with TDM as intervention registered on WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov).

The sphere of WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov) covers most parts of the world. Majority of the trials were conducted within one country. One inherent limitation of TDM is laboratory to laboratory variations in reports. Taking into account racial differences at the same time, there is still much room for development of international multi-center trials.

Most of the trials conducted in China, West Europe, United States and Australia. These countries or regions are all super power or developed countries and put great emphasis on scientific research. With a large population, they invested a lot of resources to propel medical progress. No statistics exists in large part of Africa and Asia, where less advance countries predominant. Hospitals and the pharmaceutical industry provide most monetary support to the trials. Generally speaking, the pharmaceutical industry funds trials that test their own products, whereas the hospital's funding strategies do not put commercial motivation as priority. TDM are usually hospital-based services. TDM is interdisciplinary and needs the close networking between clinicians, pharmacists, nurses and technician [7–9]. TDM procedures include request for drug concentration quantification, protocol design, biological sample collection, storage and shipment, laboratory measurements and quality control, result interpretation, and clinical decision-making requests. Apparently, most of the investigators of the included clinical trials get monetary support from their working hospitals to implement the trial. By and large, the pharmaceutical industry reluctant to do TDM because it is felt that it increases drug-associated costs and raises threshold to the success of their drug [10]. Research funds from governments, charities, societies, and foundations occupied a little part. From 2002, the number of clinical trials with TDM as intervention increased gradually with fluctuations. But each year the number of new registered trials is no more than 25. Compared with hundreds of thousands of trials in the registry platform, TDM trials are minor specialty. We may infer from the results that the utility of TDM is not prevalent in clinical practice, and only a few hospitals routinely provide these measurements. These hospitals are possibly be top-level university affiliated hospitals or research-oriented hospitals. It is urgently need to foster closer collaborations among hospital, industry, government, and other concerned parties to propel the development of TDM research.

Among the 173 clinical trials, 82.7% were interventional trials, but only 20.9% of the studies used blind masking. Insufficient blinding is not surprising, because in most cases it is not easy to use blinding in implementing TDM. Concededly, randomized controlled trials (RCTs) is the ideal method to test safety and effectiveness of interventions and obtaining convincing experimental findings [11]. Moreover, the trial design with insufficient randomization and no masking may lead to a deviation between the intervention effect and the expected results of clinical trials. Therefore, we must continue to strive to improve the quality of clinical trial design.

TDM can be applied in various medical conditions. In this study, we found that clinical trials with TDM as intervention were distributed in 14 categories in ICD-10, which were largely in infectious or parasitic disease and neoplasms. Not all medications require therapeutic monitoring. For most drugs on the market, acceptable effective and safe results can be achieved without TDM. The suitable candidate drug for TDM meets the following criteria [12]: (1) a reasonable relationship between drug concentrations and clinical effects; (2) patients' compliance concerns;



**Fig. 5.** Study design of included clinical trials (top: study type, middle left: study phase, middle right: intervention model, bottom left: allocation, bottom right: masking).

(3) drugs with narrow therapeutic index (NTI); (4) wide variation in metabolisms of drugs.

In the era of evidence-based medicine, clinical trials lay the foundation for prevention and treatment recommendations. Various organizations have laid down guidelines for TDM. Vancomycin is a glycopeptide antibiotic with an activity against Gram-positive bacteria [13], comprising the methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin notoriously has a NTI [14]. This study results show that vancomycin is the most monitored drug in TDM intervened clinical trials, though it has been on the market for decades, it is still the research hotspot. Vancomycin TDM is increasingly used as a tool to guide therapy, there are special guidelines about vancomycin TDM [15,16].

In the field of solid organ transplantation, TDM is now considered

standard practice during the treatment with most immunosuppressive agents [17]. Immunosuppressants usually have NTI and interaction with other drug, and need long-term medication, which may cause serious adverse reaction. Cyclosporin A (CsA) is the first calcineurin inhibitor (CNI) and the first immunosuppressant to follow the principle of TDM in transplantation, which undoubtedly improves the effectiveness and safety of CsA treatment. Nowadays in addition to CsA, TDM is routinely performed after transplantation for tacrolimus and sirolimus etc. Each transplant recipients have unique attributes and personalized immunosuppression management based on TDM has shown great promise [2].

Tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitor is another drug category under immunosuppressants. Monoclonal antibodies targeting TNF- $\alpha$  are the oldest and most widely used biologics and were applied to cope

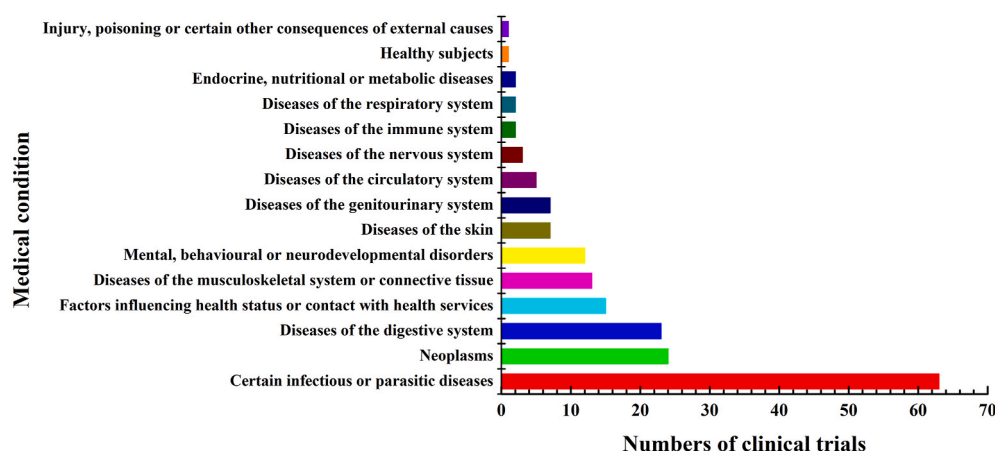


Fig. 6. Medical condition of included clinical trials.

with inflammatory bowel disease (IBD), inflammatory rheumatic diseases (RA) and so on. Although effective, they are costly [18] and about 33% of patients receiving these therapies have no response or lose initial response. The possible reason is sub-therapeutic serum drug levels or antidrug antibody (ADA) formation, which compromised the drug efficacy and induces adverse events [19,20]. TDM for TNF- $\alpha$  inhibitor involves measuring serum trough drug concentration and ADA concentrations. TDM recently garnered much attention as a very important tool in optimizing the management of patients with inflammatory disease and subsequently improving their outcomes [21].

Beta-lactams are often used as first-line treatment for infections that are difficult to treat, like sepsis, and bone infections [22]. Beta-lactams antibiotics demonstrate time-dependent bactericidal activity, and have been administered as a continuous infusion instead of traditional intermittent bolus [23] in such patients, hence dose optimization is crucial. The longer and higher beta-lactam exposures have been associated neurotoxicity development, such as seizures [24]. TDM of beta-lactams may be useful in maximizing efficacy and reducing toxicity, and can also be useful in populations with altered pharmacokinetics and pharmacodynamics (PK/PD), such as obese, elderly, or burn patients [25,26].

From this study we know that TDM can be applied to both chemical drugs and biological drugs. And biological drugs get much attention in recent years. As more and more new drugs are being approved for marketing, a few of the new drugs may be candidate for TDM, for example, pembrolizumab and dasatinib, which were granted within recent years, appeared in this statistic results.

Drug level is the most concerned outcome measure. It directly reflects the drug intervention efficacy. Current analytical techniques like spectrophotometry, chromatography, radio immunoassay, and enzyme immune assay are able to quantify the amounts of drugs in biological samples. They are not very sophisticated to use and have high sensitivity and low detection limit. Unfortunately, the actual drug concentration assay cannot be always realized, for example, the anti-tumor drug concentration in solid tumors, which is the drugs that actually works, cannot be easily determined, hence surrogate endpoints are implemented. Biomarkers are the most important endpoint for monoclonal antibody clinical study. Presence of ADA are measured in patients receiving a biological agent. Since the monitored drugs usually have narrow therapeutic range, adverse events are necessarily to be recorded to be watched closely for excessive side effects or symptoms of toxicity. Patients' attitude to TDM and cost of TDM are related to whether TDM is feasible. Frequent sampling is a realistic concern in TDM, and it will

affect the acceptance of patients. An increasing number of clinical decision support tools rely on Artificial intelligence (AI) and machine learning (ML) techniques have been successfully used to predict concentrations of drugs. Non-invasive or limited invasive sampling may further increase the applicability of TDM. For example, micro-sampling techniques such as dried blood spot (DBS) and volumetric absorptive micro-sampling (VAMS) are an increasingly popular technique in patients with limited vascular access such as neonates and patients on dialysis. The new technology may revolutionize the whole prospects of TDM. The cost of TDM is closely related to whether the patients have the desire and ability to afford it. With some drugs really expensive, cost-effectiveness studies analyzing empiric drug therapy against TDM-guided drug therapy should be encouraged to do to make conclusion that whether TDM reduces costs in healthcare systems. Most of the trials were not posted with results, thus the several available clinical trials results were not summarized and analyzed.

In addition, the sample size of 30.6% of the trials not exceed 50. It is well recognized that results from large-scale multicenter trials are more reliable and credible. Other than 89.6% trials recruiting both gender patients, there are trials only include male or female subjects, e.g. TDM guided tamoxifen treatment for women breast cancer. When comes to subjects' age, the majority of trials explored the use of TDM in  $\geq 18$  years old adults. There are diversity in the disease management and physiological conditions between children, adults and old people [27]. Alterations of PK/PD in the critically ill, obese, pregnant or lactating women, and very young or very old people are important consideration. Evidence of effects of hepatic and renal impairment on the PK of targeted drugs is limited, conflicting, or even nonexistent [28–30]. Thus, TDM clinical trial should cover more physiological condition and more age groups [31].

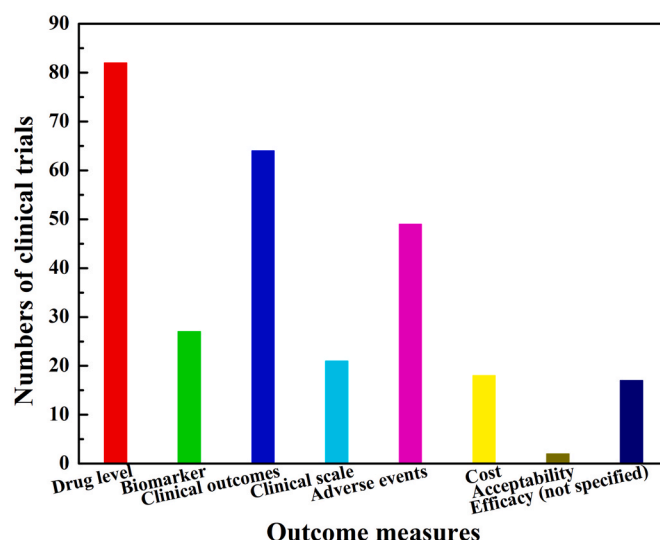
In general, this study mainly investigated the characteristics of clinical trials with TDM as intervention registered on WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov). The results suggested that most of the trials were hospital funded small size, randomized, parallel assignment, open label interventional study. Infectious or parasitic disease and neoplasms were the most concerned medical condition and immunosuppressants include selective immunosuppressants and TNF- $\alpha$  inhibitors as well as  $\beta$ -lactam antibacterials were the primarily studied drugs. Drug level is the most used endpoint. In addition, more efforts should be made to improve the quality of clinical trials, and strive for more monetary support from industry, government, societies etc.

It is undeniable that this study has some limitations. Firstly, the results may not be complete and precise due to some key information in

**Table 2**  
Monitored drugs of included clinical trials.

Drug categories	Drugs (number of clinical trials)
Alkylating agents (antineoplastic agents)	Busulfan (2), Cyclophosphamide (1)
Anesthetics	Propofol (1)
Aminoglycoside antibacterials	Amikacin (2), Arbekacin (1), Gentamicin (1), Tobramycin (1)
Anticholinesterases	Donepezil (1)
Anti-dementia drugs	Memantine (1)
Antidepressants	Venlafaxine (1)
Antiepileptics	New generation antiepileptics (1), Carbamazepine (1), Phenytoin (1)
Anti-inflammatory agents	Mesalamine (1), Sulfasalazine (1)
Antimalarials	Hydroxychloroquine (1)
Antimetabolites (antineoplastic agents)	Thioguanine (1), Fluorouracil (4), Capecitabine (1), Fludarabine (1), Mercaptopurine (1), Methotrexate (5)
Antimycotics	Anidulafungin (1), Voriconazole (8), Posaconazole (3)
Antineoplastic agents (natural product)	Paclitaxel (1)
Antipsychotics	Aripiprazole (1), Lithium (1), Risperidone (2), Sulpiride (1), Olanzapine (1)
Anti-rheumatic drugs	Not mentioned <sup>a</sup> (1)
Antithrombotic agents	Rivaroxaban (1)
Anti-tuberculosis drugs	Isoniazid (1), Rifapentine (1), Not mentioned (1)
Antivirals for treatment of HCV infections	Ribavirin (1)
Antivirals for treatment of HIV infections	Lopinavir (6), Not mentioned (2)
Anxiolytics	Diazepam (1)
β-lactam antibacterials	Amoxicillin (1), Benzylpenicillin (1), Imipenem/Cilastatin (1), Meropenem (4), Piperacillin/Tazobactam (7), Cefazolin (1), Cefotaxime (1), Ceftriaxone (1), Not mentioned (4)
Cardiac glycosides	Digoxin (3)
Corticosteroids	Budesonide (1), Prednisone (1)
Drugs used in opioid dependence	Methadone (1)
Glycopeptide antibacterials	Teicoplanin (1), Vancomycin (16)
Hormone antagonists	Tamoxifen (2)
Hypnotics and sedatives	Midazolam (1)
Selective immunosuppressants	Abatacept (2), Baricitinib (1), Cyclosporine A (3), Eculizumab (1), Sirolimus (1), Tacrolimus (11), Tofacitinib (1), Upadacitinib (1), Vedolizumab (2), Mycophenolate Mofetil (2), Leflunomide (2)
Interleukin inhibitors (immunosuppressants)	Brodalumab (1), Guselkumab (1), Ixikizumab (2), Risankizumab (1), Secukinumab (3), Tocilizumab (5)
PD-1/PDL-1 inhibitors (antineoplastic agents)	Pembrolizumab (1)
Peripheral opioid receptor antagonists	Suboxone/Naloxone (1)
Phosphodiesterase inhibitors	Milrinone (1)
Polymyxins	Colistin (2), Polymyxin B (2)
Protease inhibitors (antivirals)	Atazanavir (2), Indinavir (1), Nelfinavir (1), Ritonavir (6), Tipranavir (1), Not mentioned (1)
Protein kinase inhibitors (antineoplastic agents)	Alectinib (1), Everolimus (3), Imatinib (1), Pazopanib (4), Sunitinib (2), Afatinib (1), Dasatinib (1), Not mentioned (2)
Quinolone antibacterials	Ciprofloxacin (2), Fluoroquinolone (1), Ofloxacin (1)
Reverse transcriptase inhibitors (antivirals)	Efavirenz (6), Lamivudine (6), Tenofovir (1)
Beta-2-adrenoreceptor agonists (drugs for obstructive airway diseases)	Formoterol (1)
Tumor necrosis factor alpha (TNF-α) inhibitors (immunosuppressants)	Adalimumab (12), Certolizumab (2), Etanercept (2), Golimumab (2), Infliximab (5)

<sup>a</sup> Detailed drug name was not mentioned.



**Fig. 7.** Outcome measure of included clinical trials.

the clinical trial records in the platform database was not reported or lack of timely update. Secondly, trials search results are dynamic, therefore, this cross-sectional study comprised a snapshot of information on registered clinical trials at a certain time. Finally, clinical trial results were not analyzed due to lack of results posted.

## 5. Conclusion

In conclusion, characteristics of 173 registered clinical trials with TDM as intervention on WHO ICTRP and [ClinicalTrials.gov](https://clinicaltrials.gov) were comprehensively analyzed and investigated in this cross-sectional study. The trials were mainly conducted in several economically prosperous regions or countries. The number of registered trials had gradually increased during the past years, but still low compared with the enormous trials on the registry platforms. Novel biological drugs have increasingly become the research hotspot. There is still room for TDM clinical trial design improvement. We expect that with abundant financial support, more high-quality large-scale, multicenter RCTs are designed and implemented to promote the development of TDM in the future. As we enter the era of precision medicine, we will be able to identify not only the best drug to be administered for certain patients, but also the most effective, safe and economic dosage strategy.

## Author contributions

Shanshan Zhao and Olga Zaytseva put forward the conception and drafted the manuscript, Xiaohong Chang and Boquan Zhang performed the trials search. Shanshan Zhao reviewed the manuscript for its intellectual content and interpretation of data. All authors approved the final draft of the manuscript.

## Funding information

China Emergency General Hospital Medical Development Research Fund (K201816).

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



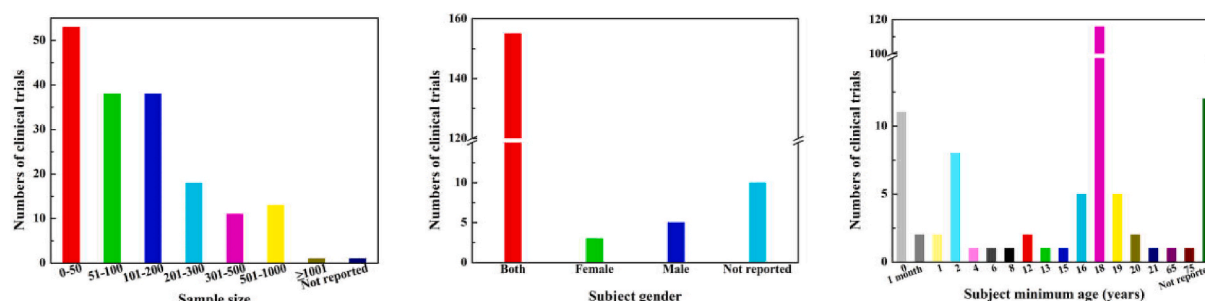


Fig. 8. Subject information of included clinical trials (left: sample size, middle: subject gender, right: subject minimum age).

## Data availability

Data will be made available on request.

## Acknowledgements

We would like to acknowledge the support provided by LiChia Chen from University of Manchester.

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