Monitoring performance of sites within multicentre randomised trials: a systematic review of performance metrics

Kate F. Walker *, Julie Turzanski, Diane Whitham, Alan Montgomery and Lelia Duley

Abstract

Background: Large multicentre trials are complex and expensive projects. A key factor for their successful planning and delivery is how well sites meet their targets in recruiting and retaining participants, and in collecting high-quality, complete data in a timely manner. Collecting and monitoring easily accessible data relevant to performance of sites has the potential to improve trial management efficiency. The aim of this systematic review was to identify metrics that have either been proposed or used for monitoring site performance in multicentre trials.

Methods: We searched the Cochrane Library, five biomedical bibliographic databases (CINAHL, EMBASE, Medline, PsychINFO and SCOPUS) and Google Scholar for studies describing ways of monitoring or measuring individual site performance in multicentre randomised trials. Records identified were screened for eligibility. For included studies, data on study content were extracted independently by two reviewers, and disagreements resolved by discussion.

Results: After removing duplicate citations, we identified 3188 records. Of these, 21 were eligible for inclusion and yielded 117 performance metrics. The median number of metrics reported per paper was 8, range 1–16. Metrics broadly fell into six categories: site potential; recruitment; retention; data collection; trial conduct and trial safety.

Conclusions: This review identifies a list of metrics to monitor site performance within multicentre randomised trials. Those that would be easy to collect, and for which monitoring might trigger actions to mitigate problems at site level, merit further evaluation.

Keywords: Multicentre, Randomised trials, Clinical trials, Performance metrics, Trial management, Site performance, Operational metrics, Key performance indicators

Background

Multicentre randomised trials are complex and expensive projects. Improving the efficiency and quality of trial conduct is important, for patients, funders, researchers, clinicians and policy-makers [1]. A key factor in successful planning and delivery of multicentre trials is how well sites meet their targets in recruiting and retaining participants, and in collecting high-quality, complete data in a timely manner [2]. Collecting and monitoring easily accessible data relevant to performance of sites has the potential to improve the efficiency and success of trial management. Ideally, such performance metrics should provide information that quickly identifies potential problems so they can be mitigated or avoided, hence minimising their impact and improving the efficiency of trial conduct.

We are not aware of any standardised metrics for monitoring site performance in multicentre trials. A recent query to all UK Clinical Research Collaboration (UKCRC), registered Clinical Trials Units (CTUs) revealed that many units routinely collect and report data for each site in a trial; such as numbers randomised, case report forms (CRFs) returned, data quality, missing primary outcome data, and serious breaches. How such data are used to assess and manage performance varies widely however [3–7]. Agreeing a small number of metrics for site performance that could be easily collected, presented and monitored in a standardised way by a trial manager or trial co-ordinator would be a potentially useful tool to improve efficient trial conduct.

* Correspondence: kate.walker@nottingham.ac.uk
Nottingham Clinical Trials Unit, QMC, Nottingham NG7 2UH, UK

© The Author(s). 2018 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Currently, trial teams, sponsors, funders and oversight committees monitor site performance and trial conduct based primarily on recruitment. Whilst clearly important, recruitment is not the only performance indicator that matters for a successful trial. Using a range of additional metrics that include data quality, protocol compliance and participant retention would give a better overall measure of the performance of each trial site, and the trial overall. To be low cost and efficient, the number of metrics monitored at any one time should be limited to no more than 8 to 12. We conducted a systematic review to identify performance metrics that have been used, or proposed, for monitoring or measuring performance at sites in multicentre randomised trials.

**Methods**

We performed a systematic review to identify metrics that have been used or proposed for monitoring or measuring performance at individual sites in multicentre randomised trials.

**Criteria for potentially eligible studies**

Studies were potentially eligible for inclusion if they:

- Reported one or more site performance metric, either used or proposed for use, specifically for the purpose of measuring individual site performance
- Were multicentre randomised trials, or concerning multicentre trials
- Were published in English
- Related to randomised trials involving humans

Studies where the strategy for monitoring site performance was randomly allocated were included. We anticipated that there might be studies where the adoption of an individual performance metric might have been tested by randomly allocating sites to using that particular metric or not. Studies relevant to both publically funded and industry-funded trials were included.

---

**Fig. 1** Flow diagram

- Records identified through database searching (n = 3365)
- Records after duplicates removed (n = 3188)
- Full-text articles excluded, (n = 3041)
- Records screened by KW and JT (n = 3188)
- Full-text articles assessed for eligibility (n = 147)
- Full-text articles excluded, (n = 124)
- Studies included in qualitative synthesis (n = 23)
### Table 1 Characteristics of included studies

| Study       | Study description                                                                 | Number of sites (sample size) | Metrics reported by each study included as site performance metric | Excluded as not site performance metric |
|-------------|-----------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------|----------------------------------------|
| Bose 2012 [14] | Paper discussing trial management through central monitoring                        | Not applicable              | • Site location potential index based on an assessment of the number of patients at an individual site with the disease of interest  
• Trial compliance index based on a number of suggested factors including the number of late visits, failure to achieve recruitment target, number of dosing errors, etc. | • Drug adversity measurement (B)  
• Drug potential index (B) |
| Djali 2010 [15] | Paper discussing a data-driven quality management system                             | Not applicable              | • Enrollment number per site  
• Recruitment period per site  
• Number of AEs per site  
• Number of protocol deviations and violations per site | • Number of discontinuations per site (A)  
• Deaths per site (D) |
| Elsa 2011 [16] | Methodology of developing 'key risk indicators' for monitoring of a large international clinical trial | Not applicable              | • Rate of SAE reporting per site: centres assigned a dichotomous score depending on whether they showed extreme deviation from comparable sites (arbitrarily defined as half the observed median rate across sites)  
• Short visit duration: centres assigned a dichotomous score depending on whether they showed extreme deviation from comparable sites (arbitrarily defined as half the observed median rate across sites) | • Measures of compliance with study treatment (A)  
• Blood results/other continuous variables examined for unusual patterns (A) |
| Glass 2007 [17] | Study analysing data retrospectively from 262 clinical trials to determine variables associated with successful trial delivery | Not applicable              | • Actual number participants randomised per site  
• Number successfully completing the study's protocol per site  
• Time between when an individual site randomises its first participant and the time the first site in that study enrolls its first patient | |
| Hanna, 2013 [11] | Development of a list of quality indicators for trial performance based on the consensus of experts | Not applicable              | • SAE reporting measured by the number of SAEs reported/number of SAEs identified in trial database or trial follow-up documents  
• Transfer of CRF to CTU measured by the number of completed CRF received by CTU within 30 days/number of completed CRF received by the CTU in 3 months | |
| Jou, 2013 [18] | Aim of the main study: treatment-naïve, hepatitis C patients randomised to two peginterferon regimens. Primary outcome virologic response. A retrospective analysis was performed of individual site performance using trial data | 118 (3070)                 | • Rates of screen failure defined as the percentage of participants screened who failed screening  
• Completion and discontinuation of treatment, defined as the percentage of participants who completed treatment/percentage of participants who discontinued treatment  
• Completion/discontinuation of follow-up, defined as the percentage who completed follow-up/percentage who discontinued follow-up | • Treatment adherence (B) |
| Khatawkar 2014 [19] | Retrospective analysis of data queries using clinical trial data                   | Not applicable              | • Data query (DQ) rate per page  
• DQ rate per page by phase of study | • DQ rate per page by country (B)  
• DQ rate per page by therapeutic area (B) |
| Lee 2012 [20]  | Paper describing the output of a Delphi survey to establish an 'evaluation framework' for clinical trial data | Not applicable              | • Rapid enrolment, defined as time taken to reach target enrolment  
• Timely data entry, defined as time taken for data entry after completion of informed consent  
• Timely manual query management, defined as time taken for response to manual query request from data centre  
• Timely database lock, defined as | • Weeks after go-live, i.e. after the point of protocol amendment (A) |
| Study | Study description | Number of sites (sample size) | Metrics reported by each study | Included as site performance metric | Excluded as not site performance metric* |
|-------|-------------------|-----------------------------|--------------------------------|-------------------------------------|----------------------------------------|
| Rojavin, 2005 [21] | Paper describing and discussing one proposed metric | Not applicable | • Recruitment Index (RI) = (LPFV − FPFV) x S/P where LPFV = date of the last participant first visit FPFV = date of the first participant first visit S = number of participating sites P = number of participants who successfully completed the study |                               |                                   |
| Rosendorf, 1993 [22] | Trials of treatment for HIV. No further details. An evaluation tool was proposed to monitor individual site performance within a multicentre randomised trial. | 59 (ns) | Intensity adjusted score (IAS) = IAS = IS0 + don x IS1 + doff x IS2 where: IS0 = score assigned for enrolling a new participant during the 6 month evaluation period don = number of days the participant was on the study medication during the evaluation period doff = number of days the participant was off the study medication IS1 = intensity score for the days in which the participant is receiving study medication IS2 = intensity score for the days in which the participant is off all study medication ISA is calculated for each participant and then summing scores across all participants, once during the evaluation period • Funding adjusted score = IAS divided by the amount awarded for total direct costs during the given time period • Summary quartiles = total number of new and continuing participants on study |                               |                                   |
| Sweetman, 2011 [23] | Retrospective analysis of publications of 80 clinical trials on protocol violations reporting | Not applicable | Occurrence of protocol violations, defined as total number of protocol violations divided by the number of enrolled participants |                               |                                   |
| Thorn, 2011 [12] | Report of a centre performance assessment tool used within a clinical trial network to assess individual site performance | Not applicable | • Protocol adherence, defined as average rate of protocol violations per enrolled participant • Data quality, defined as average rate of edit checks per participant • Data timeliness, defined as the percentage of forms entered late • Time of starting after the first centre start date • Sum of protocol adherence, data quality, data timeliness and timeliness of study start-up to give overall rank • Timeliness of study start-up |                               |                                   |
| Tudur Smith, 2014 [24] | Paper describing monitoring methods using a ‘risk proportionate approach’ used by an individual clinical trials unit | Not applicable | • Consent form completion, defined as consent forms returned within 7 days of completion by sites. |                               |                                   |

*Table 1 Characteristics of included studies (Continued)
### Table 1 Characteristics of included studies (Continued)

| Study | Study description | Number of sites (sample size) | Metrics reported by each study | Excluded as not site performance metric |
|-------|-------------------|------------------------------|--------------------------------|----------------------------------------|
|       |                   |                              |                                |                                        |
| Wilson, 2014 | Theoretical paper describing methods of monitoring the conduct of trials | Not applicable | • Recruitment process, defined as frequency of eligible participants who do not provide consent <br> • Missing primary outcome data, defined as cumulative percentage of participants with missing primary outcome data at each site <br> • SAEs, defined as cumulative percentage of participants with at least one SAE across the trial as a whole and at each site / measure of time, e.g. 1 month <br> • Sum of all SAEs/sum of all follow-up for the trial <br> • Sum of all follow-up at site x overall SAE rate for the trial <br> • Visit dates, defined as time between actual date of visit versus expected date of visit | • Quality metric encompassing: average number of major audit findings per audited site; percentage per site of unreported, confirmed SAEs; number of significant protocol deviations per site <br> • Frequency of protocol violations for eligibility criteria and randomisation per site <br> • Rates of withdrawal by site |
| Berthon-Jones 2015 | Aim of main study: treatment-naive HIV patients randomised to 2 different types of ART. Primary outcome plasma HIV-RNA, change from baseline to week 48. Performance across 5 geographical regions was assessed using performance metrics | 36 (322) | • Time from protocol release to ethics/ regulatory submission <br> • Time from protocol release to ethics/ regulatory approval <br> • Time from protocol release to first participant randomised (FPR) <br> • Time from protocol release to last participant randomised (LPR) <br> • Time from site opened to first participant randomised (FPR) <br> • Time from site opened to last participant randomised (LPR) <br> • Actual versus estimated recruitment <br> • Time from participant visit to electronic data capture (EDC) initiation <br> • Time from EDC initiation to completion <br> • Number of missing values per participant <br> • Number of data queries per participant <br> • Number of SAEs reported per participant <br> • Time from SAE occurrence to initial report <br> • Time from initial SAE report to final report <br> • Number of samples collected versus number required by protocol | • Number of missed visits per region (B) <br> • Quality of laboratory sample/s collected (A) <br> • Number of plasma samples collected versus protocol-mandated samples to be collected (C) <br> • Number of buffy-coat samples collected versus protocol-mandated samples to be collected (C) |
| Katz, 2015 | Aim of main studies: osteoarthritis (2 trials), lower back pain (1 trial) randomised to fulranumab infusion or placebo. Primary outcomes unspecified. Within these three clinical trials a method of monitoring individual site performance was applied | 40–88 (91–157) | • Time to data query response | • Compliance with study drug (D) |
| Kim, 2011 | Aim of main study: patients with acute cerebral haemorrhage randomised to early intensive antihypertensive or standard regimen. Primary outcome death or disability at 3 months. A site performance monitoring tool was incorporated for monitoring individual site performance during the trial | 100 (1280) | • Participant recruitment per site <br> • CRF data collection timeliness + completeness <br> • Protocol violations per site <br> • SAE reporting per site | • Participant study progress (A) <br> • Site data monitoring visit findings (A) <br> • Data clarification request processing (A) <br> • Regulatory document collection and tracking (A) |
| Rifkind, 1983 | Aim of the main study: men with primary type 2 hyper-lipoproteinemia randomised to bile acid sequestrant or placebo. Primary outcome CHD death and/or nonfatal myocardial infarction. Within this study measures of individual site recruitment performance were monitored. | 12 (3550) | • Proportion of initial contacts proceeding to first protocol visit by recruitment source <br> • Proportion of first protocol visits proceeding to study entry by recruitment source | • Quality of laboratory sample/s collected (A) <br> • Number of plasma samples collected versus protocol-mandated samples to be collected (C) |
**Search strategy**

We searched the Cochrane Library and five biomedical bibliographic databases (CINAHL, Excerpta Medica database (EMBASE), Medical Literature Analysis and Retrieval System Online (Medline), Psychological Information Database (PsychINFO) and SCOPUS) and Google Scholar from 1980 to 2017 week 07. The search strategy is provided as an Appendix (Table 3).

**Selection of studies**

Two reviewers (KW, JT) independently assessed for inclusion the titles and abstracts identified by the search strategy. If there was disagreement about whether a record should be included, we obtained the full text.

We sought full-text copies for all potentially eligible records, and two reviewers (KW, JT) independently assessed these for inclusion. Disagreements were resolved by discussion, and if agreement could not be reached the study was independently assessed by a third reviewer (LD). Multiple reports of the same study were linked together.

**Data extraction and data entry**

Two reviewers (KW, JT) extracted data independently onto a specifically designed data extraction form. In the few cases where full text was not available (n = 9), data were extracted using the title and abstract only. Data were entered into an Excel spreadsheet, and checked.

Data were extracted on the design of the randomised trial (participants, intervention, control, number of sites and target sample size); whether the performance metric/s was theoretical or applied. For each performance metric we collected data that included: a verbatim description of the metric; how the metric was measured or expressed; timing of the measurement and during which phase of the study; and whether the metric was included as a site performance metric or excluded as not a site performance metric.

| Study                | Study description                                                                 | Number of sites (sample size) | Metrics reported by each study                                      | Excluded as not site performance metric |
|----------------------|-----------------------------------------------------------------------------------|-------------------------------|---------------------------------------------------------------------|----------------------------------------|
| Saunders, 2015 [29]a | Aim of the main study: critical care patients randomised to probiotic or placebo, primary outcome ventilator associated pneumonia. Within this study the team focused on screening performance in individual centres | 14 (285)                      | - Non-screening weeks = proportion of weeks during which participants were not screened for trial eligibility | -                                     |
| Sun, 2008 [30]       | Aim of the main study: patients with major depression randomised to aprepitant or placebo, primary outcome change in Hamilton Depression Scale. Within this study measures of individual site performance were captured | Not reported                  | - Administration excellence, defined as site administration performance and interaction with central study team rated 1, 2 or 3 | - Level of medication non-compliance, defined as the mean number of doses of study-assigned medication (B) |
| Wear, 2010 [31]a     | Aim of the main study: patients with multiple myeloma, multiple clinical trials. No further details. Performance metrics utilised during the study | Not reported                  | - First patient dosed (FPD), defined as time from receipt of final protocol to the first participant treated | - Baseline enrolment timeline (BET), defined as target time period to obtain EC |

*AE adverse event; ART antiretroviral therapy; CHD coronary heart disease; CRF case record form; CTU clinical trial unit; ns not specified; SAE serious adverse event; VTE venous thromboembolism*

*a Excluded due to (a) lack of clarity, (b) not related to individual site performance, (c) too specific to an individual trial methodology, (d) pertaining to clinical outcomes not trial performance*

*b It is unclear from the paper whether enrolment refers to participants randomised to a study or simply consented and then screened for study eligibility*
who measured the metric; if a threshold exists to trigger action, what the threshold was and what action it triggers; and whether the metric was recommended by the authors.

Data analysis
We described the flow of studies through the review, with reasons for being removed or excluded, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [10]. Characteristics of each study were described and tabulated. Analyses were descriptive only, with no statistical analyses anticipated.

Results
The database search identified 3365 records, of which 177 were duplicates, leaving 3188 screened for eligibility (Fig. 1). At screening, we obtained full-text copies for 147 records to determine eligibility. For a further seven records full-text copies were unavailable, and so screened was based on the abstract only. Of those full-text copies and abstracts (for papers where the full text was unavailable), there was disagreement on three papers. Following discussion two papers were accepted for inclusion [11, 12] and one paper was excluded [13].

Twenty-one studies were agreed for inclusion, of which 14 were studies proposing performance metrics and seven were studies using performance metrics (Table 1). These 21 studies reported a total of 117 performance metrics. The median number of performance metrics reported per study was 8, with the range being 1–16. Those 117 metrics were then screened, to exclude any judged as: lacking sufficient clarity; being unrelated to individual site performance; being too specific to an individual trial methodology or pertaining to clinical outcomes not trial performance. This left 87 performance metrics to be considered for use in day-to-day trial management. The metrics broadly fell into six main categories: assessing site potential before recruitment starts; and monitoring recruitment, retention, quality of data collection, quality of trial conduct, and trial safety (Table 2).

Discussion
As far as we are aware, this is the first systematic review to identify and describe proposed or utilised metrics to monitor site performance in multicentre randomised trials. It provides a list of performance metrics, which can be used to contribute to developing and agreed a proposed set of performance metrics for use in day-to-day trial management. We identified 87 performance metrics which fell broadly into six main categories.

A strength of our study was the comprehensive search of the literature.

In planning this systematic review we envisaged that studies would be identified that had evaluated individual performance metrics either by implementation mid-way through a study, or ideally by randomising individual sites to use of a particular metric or not. Unfortunately, there was a paucity of such studies. Most studies suggested performance metrics on a purely theoretical basis, and did not provide data on the actual use of suggested metrics. The main limitations of our study were the lack of studies implementing performance metrics and reporting the effects of their utilisation, and that published work on this topic is limited, which is perhaps surprising as informal assessment of how sites perform in multicentre trials is common.

This list of performance metrics contributed to development of a Delphi survey sent to trial managers, UKCRC CTU directors and key clinical trial stakeholders, which is reported elsewhere. They were invited to participate through the UK Trial Managers’ Network (UK TMN) and UK Clinical Research Collaboration (UKCRC CTU) Network. Three Delphi rounds were used to steer the groups to consensus, refining the list of performance metrics. The reasons for their decisions were documented. Finally, data from the Delphi survey was presented to stakeholders in a priority setting expert workshop, providing participants with the opportunity to express their views, hear different perspectives and think more widely about monitoring of site performance. This was used to establish a consensus among experts on the top key performance metrics, expected to number around 8–12.

Conclusions
This study provides trialists for the first time with a comprehensive description of performance metrics described in the literature that have been proposed or used in the context of multicentre randomised trials. It will assist future work to develop a concise, practical list of performance metrics which could be used in day-to-day trial management to improve the performance of individual sites. This has the potential to reduce both the financial cost of delivering a multicentre trial, and the research waste and delay in scientific progress that results when trials fail to meet their recruitment target, are poorly conducted, or have inadequate data.

| Categories                              | Example performance metric                                      | Studies in which metric included |
|-----------------------------------------|-----------------------------------------------------------------|---------------------------------|
| Assessing site potential                | Site location potential index based on an assessment of the number of patients at an individual site with the disease of interest | [14]                            |
| Monitoring recruitment                  | Number of participants randomised per site                      | [15, 17, 27]                    |
| Monitoring retention                    | Rates of withdrawal by site                                     | [20, 25]                        |
| Quality of data collection              | Number of data queries per participant                         | [2, 12, 19]                     |
| Trial conduct                           | Protocol violations per site or per participant                 | [12, 15, 23, 27, 30]            |
| Trial safety                            | Serious adverse event (SAE) reporting per site                  | [11, 24, 27]                    |
Appendix

Table 3  Search strategy. Monitoring performance of sites within multicentre randomised trials: a systematic review of performance metrics

| #  | Searches                                                                 |
|----|--------------------------------------------------------------------------|
|  1 | Randomised, controlled trial                                             |
|  2 | Clinical trial                                                           |
|  3 | Pragmatic trial                                                          |
|  4 | Controlled clinical trial                                                |
|  5 | 1 or 2 or 3 or 4                                                         |
|  6 | Performance indicator                                                    |
|  7 | Performance metric                                                       |
|  8 | Performance measure                                                      |
|  9 | Enrollment rate                                                          |
| 10 | Participant enrollment                                                   |
| 11 | Participant recruitment                                                  |
| 12 | Quality indicator                                                        |
| 13 | Quality measure                                                          |
| 14 | Performance management                                                   |
| 15 | Assessing site performance                                               |
| 16 | Central monitoring                                                       |
| 17 | Clinical trial monitoring                                                |
| 18 | Clinical trial reporting                                                 |
| 19 | Trial analytics                                                          |
| 20 | Trial management                                                         |
| 21 | Site performance                                                         |
| 22 | Study conduct                                                            |
| 23 | Trial site performance                                                   |
| 24 | Benchmarking performance                                                 |
| 25 | Clinical data management                                                 |
| 26 | Clinical trial data quality                                               |
| 27 | Laboratory sample quality in clinical trials                             |
| 28 | Operational metrics                                                      |
| 29 | Operational performance                                                  |
| 30 | Performance evaluation                                                   |
| 31 | Performance monitoring                                                   |
| 32 | Performance score                                                        |
| 33 | Protocol deviations                                                      |
| 34 | Protocol violations                                                      |
| 35 | Quality management system                                                |
| 36 | Recruitment index                                                        |
| 37 | Screening logs                                                           |
| 38 | Strategic project management                                             |
| 39 | 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or |
|   | 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28或 29 or 30 or 31 or |
|   | 32 or 33 or 34 or 35 or 36 or 37 or 38                                    |

(Continued)

| #  | Searches                                                                 |
|----|--------------------------------------------------------------------------|
| 40 | 39 and S                                                                 |
| 41 | 40 Not (animals/ not humans.sh.)                                         |
| 42 | 40                                                                        |
| 43 | Limit 42 to English language                                             |
6. Timmermans C, Venet D, Burzykowski T. Data-driven risk identification in phase III clinical trials using central statistical monitoring. Int J Clin Oncol. 2016;21(1):38–45.

7. Tantsyura V, Dunn IM, Fendt K, Kim YJ, Waters J, Mitchel J. Risk-based monitoring: a closer statistical look at source document verification, queries, study size effects, and data quality. Ther Innov Regul Sci. 2015;49(6):903–10.

8. Smith B, Martin L, Martin S, Denslow M, Hutchens M, Hawkins C, Panier V, Ringel MS. What drives site performance in clinical trials? Nat Rev Drug Discov. 2018;17(6):389–90.

9. Dorrnott K. Using metrics to direct performance improvement efforts in clinical trial management. Monitor. 2012;26(4):9–13.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. J Clin Epidemiol. 2009;62(10):1006–12.

11. Hanna M, Minga A, Fau P, Borand L, Douf A, Mbem JM, Gad RR, Anglaret X, Bazin B, Chene G. Development of a checklist of quality indicators for clinical trials in resource-limited countries: The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) experience. Clin Trials. 2013;10(2):300–18.

12. Thom E. A center performance assessment tool in a multicenter clinical trials network. Clin Trials. 2011;8(4):519.

13. Hullsiek KH, Wyman N, Kagan J, Grup J, Carey C, Hudson F, Finley E, Belloso W. Design of an international cluster-randomized trial comparing two data monitoring practices. Clin Trials. 2013;10:532–3.

14. Bose A, Das S. Trial analytics—A tool for clinical trial management. Acta Poloniae Pharmaceutica - Drug Research. 2012;69(3):523–33.

15. Qajl S, Jansens S, Van Yperen S, Van Panjsh J. How a data-driven quality management system can manage compliance risk in clinical trials. Drug Inform J. 2010;44(4):359–73.

16. Elia VM, Jemma HC, Martin L, Jane A. A key risk indicator approach to central statistical monitoring in multicentre clinical trials: method development in the context of an ongoing large-scale randomised trial. Trials Conference: Clinical Trials Methodology Conference. 2011;121.

17. Glass HE, DiFrancesco JJ. Understanding site performance differences in multinational phase III clinical trials. Int J Pharmaceutical Med. 2007;21(4):279–86.

18. Jou JH, Sulkowski MS, Noviello S, Long J, Pedicone LD, McHutchison JG, Muir AJ. Analysis of site performance in academic-based and community-based centers in the IDEAL study. J Clin Gastroenterol. 2013;47(10):e91–5.

19. Khatawak S, Bhatt A, Shetty R, Shilpa P. Analysis of data query as parameter of quality. Perspect Clin Res. 2014;5(3):121–4.

20. Lee HJ, Lee S. An exploratory evaluation framework for e-clinical data management performance. Drug Inf J. 2012;46(5):555–64.

21. Rojavin MA. Recruitment index as a measure of patient recruitment activity in clinical trials. Contemp Clin Trials. 2005;26(5):552–6.

22. Rosendorf LL, Dafni U, Amato DA, Lunghofer B, Bartlett JG, Leedom JM, Wara DW, Armstrong JA, Godfrey E, Sukkestad E, et al. Performance evaluation in multicenter clinical trials: Development of a model by the AIDS Clinical Trials Group. Control Clin Trials. 1993;14(6):523–37.

23. Sweetman EA, Doig GS. Failure to report protocol violations in clinical trials: a threat to internal validity? Trials. 2011;12:214 (no pagination).

24. Tudur Smith C, Williamson P, Jones A, Smyth A, Hewer SL, Gamble C. Risk-proportionate clinical trial monitoring: an example approach from a non-commercial trials unit. Trials. 2014;15(1):127 (no pagination).

25. Wilson B, Provencher T, Gough J, Clark S, Abdachitov R, de Roek K, Constantine SJ, Kneppe D, Lawton A. Defining a central monitoring capability: sharing the experience of TransCelerate BioPharma’s approach, Part 1. Ther Innov Regul Sci. 2014;48(5):529–35.

26. Katz N. Development and validation of a clinical trial data surveillance method to improve assay sensitivity in clinical trials. J Pain. 2015;15:588.

27. Kim J, Zhao W, Pauls K, Goddard T. Integration of site performance monitoring module in web-based CTMS for a global trial. Clin Trials. 2011;8(4):450.

28. Rifkind BM. Participant recruitment to the coronary primary prevention trial. J Chronic Dis. 1983;36(6):451–65.

29. Saunders L, Clarke F, Hand L, Jakab M, Watpool I, Good J, Heets-Ansdel D. Screening weeks: a pilot trial management metric. Crit Care Med. 2015;1330.

30. Sun J, Wang J, Liu G. Evaluation of the quality of investigative centers using clinical ratings and compliance data. Contemp Clin Trials. 2008;29(2):252–60.

31. Wear S, Richardson PG, Reyta C, Vij R, Fiala M, Lorial S, Francis D, DGCapua Siegel DS, Schramm AA, Jakubovskj A, et al. The multiple myeloma research consortium (MMRC) model: Reduced time to trial activation and improved accrual metrics. Blood Conference: 52nd Annual Meeting of the American Society of Hematology. ASH. 2010;116(21):3803.