Journal of Clinical Epidemiology 91 (2017) 6–12

Journal of Clinical Epidemiology

SERIES: PRAGMATIC TRIALS AND REAL WORLD EVIDENCE

Series: Pragmatic trials and real world evidence: Paper 7. Safety, quality and monitoring

Elaine Irving[a,*], Rutger van den Bor[b,c], Paco Welsing[b], Veronica Walsh[d], Rafael Alfonso-Cristancho[e], Catherine Harvey[f], Nadia Garman[a], Diederick E. Grobbee[b,c], on behalf of GetReal Work Package 3

[a]*Real World Study Delivery, WW RWE & Epidemiology, GSK R&D, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NJ*
[b]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, GA 3508, Utrecht, The Netherlands*
[c]*Julius Clinical, Academic Research Organization, Broederplein 41-43, Zeist 3703 CD, The Netherlands*
[d]*Medical Affairs Operations, Janssen-Cilag S.A., 1 rue Camille Desmoulins, 92787 Issy-les-Moulineaux, Cedex 9, France*
[e]*Value Evidence & Outcomes, GSK R&D, 1250 S. Collegeville Road, Collegeville, PA 19426, USA*
[f]*Global Clinical Safety & Pharmacovigilance, GSK R&D, Iron Bridge Road, Stockley Park West, Uxbridge, Middlesex UB11 1BT, UK*

Accepted 3 May 2017; Published online 11 May 2017

Abstract

Objective: Pragmatic trials offer the opportunity to obtain real-life data on the relative effectiveness and safety of a treatment before or after market authorization. This is the penultimate paper in a series of eight, describing the impact of design choices on the practical implementation of pragmatic trials.

Study Design and Setting: This paper focuses on the practical challenges of collecting and reporting safety data and of monitoring trial conduct while maintaining routine clinical care practice.

Conclusion: Current ICH guidance recommends that all serious adverse events and all drug-related events must be reported in an interventional trial. In line with current guidance, we propose a risk-based approach to the collection of non–drug-related non–serious adverse events and even serious events not related to treatment based on the risk profile of the medicine/class in the patient population of interest. Different options available to support the collection and reporting of safety data while minimizing study-related follow-up visits are discussed. A risk-based approach to monitoring trial conduct is also discussed, highlighting the difference in the balance of risks likely to occur in a pragmatic trial compared to traditional clinical trials and the careful consideration that must be given to the mitigation and management of these risks to maintain routine care.

Keywords: Pragmatic trial; Safety reporting; Monitoring; Adverse drug reaction; Adverse event; Routine care

1. Introduction

Pragmatic trials are usually conducted to demonstrate the real-world effectiveness, safety or health-economic benefits of a new medicine, an existing medicine for a new indication, behavioral/surgical interventions, or diagnostic tests in routine clinical practice [1]. The potential to demonstrate such real-world effects heavily relies on the willingness of patients and treating physicians to participate in this type of research [2,3] and also on the ability to maintain routine clinical practice (to the extent possible) throughout the duration of the trial. However, this can be challenging due to the regulatory requirements imposed on interventional studies that involve the random assignment of patient to a particular therapy [4]. The collection of adverse events (AE) and the monitoring of trial conduct to ensure that the trial is conducted, recorded, and reported according to good clinical practice (GCP) may impact routine clinical care. This, in turn, would mean that data are not really representative of the real-life clinical situation, and generalizability of trials results may be compromised [5,6].

However, the nature and extent of AE collection and monitoring of trial conduct can be dependent on the specifics of the study. For example, the concept of "low interventional trials" will be introduced in the new European clinical trial regulation [7]. These regulations relate to investigational medicinal products used according to their marketing

* Corresponding author. Tel.: +44-(0)-7500765703.
E-mail address: elaine.a.irving@gsk.com (E. Irving).

http://dx.doi.org/10.1016/j.jclinepi.2017.05.004

What is new?

Key findings

- Current ICH Guidance states that all serious adverse events and all drug-related events must be collected and reported to the study sponsor in an interventional trial. The decision on whether or not to collect non–serious adverse events should be based on knowledge of the safety profile of the medicine and medicine class in the patient population that is examined.
- The greatest challenge with respect to the collection of safety data in a pragmatic trial is to establish a process that supports the timely collection and reporting of safety data with sufficient detail while minimizing the number of follow-up visits beyond the visits that are part of usual care.
- The balance of risks and potential impact in a pragmatic trial will be different from a traditional randomised controlled trial (RCT). The main consideration in a monitoring plan for a pragmatic trial is defining how to manage the risks in a way that does not interfere with routine care or the objectives of the study. Where possible centralized risk-based monitoring is recommended for pragmatic trials to minimize interference with clinical practice and patient care.

What this study adds to what was known?

- This article discusses different options available for collecting safety data and data required to monitor pragmatic trial conduct.

What is the implication and what should change now?

- Whatever approach is taken for collecting safety data and monitoring trial conduct in a pragmatic trial it is likely to be ‘‘nonstandard’’ compared to an explanatory trial and will therefore require early and detailed discussions with ethics review boards and regulatory authorities in all participating countries.

Box 1 Series on pragmatic trials

Pragmatic trials aim to generate real-world evidence on the (relative) effects of treatments, generalizable to routine practice. In this series, we will discuss options and choices for pragmatic trial design, operational consequences, and the interpretation of results.

1. Introduction
2. Setting, sites, and investigator selection
3. Patient selection challenges and consequences
4. Informed consent
5. Usual care and real life comparators
6. Outcome measures in the real world
7. **Safety, quality and monitoring**
8. Data collection and management

authorization or for which the use is evidence based. In addition, the The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have stressed the need for developing more risk-based approaches toward the monitoring of trial conduct. These concepts provide an opportunity for a more proportionate approach to the collection of safety data and the monitoring of trial conduct that may be suitable for pragmatic trials. The present paper discusses the main operational challenges in specifying a safety monitoring plan and a trial monitoring plan for pragmatic clinical trials (Box 1).

1.1. Collection and reporting of safety events

Current international guidelines on GCP state that all serious adverse events (SAEs) must be collected in an interventional trial and reported within 24 hours to the trial sponsor unless specified otherwise in the study protocol [8]. The collection and reporting of non-SAEs can be tailored under certain conditions, for instance, if a significant amount of safety data is already available as is the case with a marketed medication [9]. Furthermore, the nature and extent of patient safety monitoring may depend on the added risks of the trial intervention relative to standard care [9]. The new European Clinical Trial Regulation moves toward further simplification and defines that the protocol may exclude certain AEs from being recorded and reported and also exclude certain SAEs from requiring immediate reporting [7]. Therefore, here, we propose that the extent to which non-SAEs should be recorded depends on whether (1) the data will be used to define the safety profile of the medication; (2) there are specific safety surveillance measures in place as part of a market authorization; (3) the medication is being used in accordance with the market authorization; (4) the safety profile of the medicine and/or class is known in the patient population under study; and (5) data are being reported by a qualified physician who determines drug relatedness and severity of any given event.

It is conceivable that only serious and non–serious adverse drug reactions (ADRs) may be collected in a pragmatic trial that examines a marketed medicine of which the safety profile has previously been described. However, it should be noted that depending on what is known about

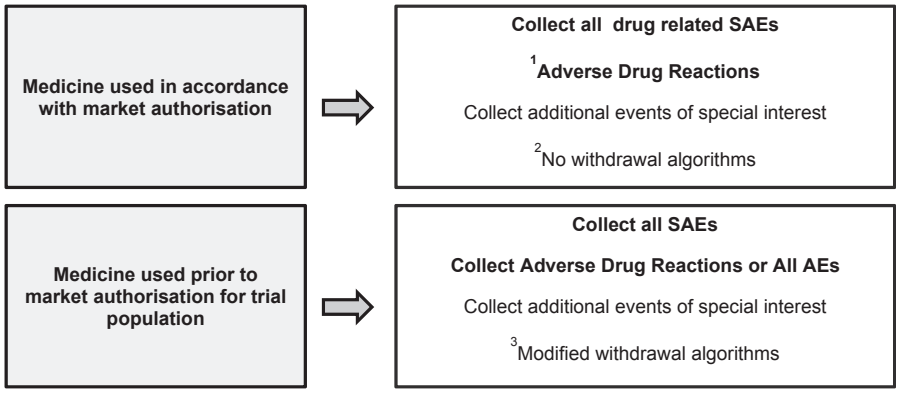

Fig. 1. Which safety events should be collected in a pragmatic trial? [1]Level of collection will depend on: objectives of the study—effectiveness or effectiveness/risk, what is known about the safety profile of the drug, postmarketing pharmacovigilance requirements, and length of time drug has been on the market; [2]Patients should be managed in accordance with standard clinical practice; there is no need to impose additional ''trial'' restrictions; [3]Modified algorithms to accommodate comorbidities in trial population, Serious adverse event (SAE): any serious medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

the medicine or class of medicines, some drug-related AEs will not be known and therefore careful consideration should be given to assessing the relatedness of AEs with the drug and the risk of missing new drug-related AEs if the decision is made not to report all AEs. In the preauthorization phase or when new indications are investigated, however, collection of all serious and non-SAEs (SAEs and AEs) may still be required (see Fig. 1). Furthermore, the higher the risks associated with the medicine and the higher the disease severity, the more frequently physicians should monitor the patients. In pragmatic trials, safety data collection should, wherever possible, be embedded within routine care visits, although it must be acknowledged that these vary widely globally according to different local practice. The frequency with which data should be collected will also depend on the level of safety information available about the medicine. The less information available or the higher the risks associated with the medicine, the more regularly physicians should monitor the patients. In cases where local norms are insufficient, visit frequency may need to be included in a protocol. The disease being studied, and trial design will also affect the frequency of data collection. More severe conditions, which are normally associated with more frequent routine monitoring by the treating physician, offer greater opportunity to also frequently collect study-related safety data in a manner that does not interfere with routine care.

1.2. The challenges of collecting and reporting AE data in pragmatic trials

As pragmatic trials investigate the effects of medication in routine care, they may include investigators who are inexperienced in conducting clinical research, AE reporting, and assessing drug relatedness. From a practical perspective of costs, time, and space, frequent trial visits may not be something the practice can easily manage and so may affect the willingness of physicians and patients to participate. Some severe conditions, such as Chronic obstructive pulmonary disease (COPD), require a high frequency of follow-up visits; however, the frequency often decreases as the control of symptoms improves, and patients may not be seen for several months. Similarly, patients with well-controlled high blood pressure may only visit their physician annually for routine check-ups, introducing the need to consider alternative methods, such as follow-up by telephone, to collect safety data. Furthermore, study patients may present themselves in a health care department or emergency room outside the scope of the investigator. This and any associated safety events may remain unreported to the patient's physician, especially with infrequent follow-up, unless it is recorded in the hospital medical records or the investigator is reminded to interview the patient on clinical events during a follow-up.

1.3. Possible approaches to the collection and reporting of AEs

Collecting safety data in a structured and complete manner is crucial to understand the course of an AE and its potential drug relatedness. The mechanism for collecting

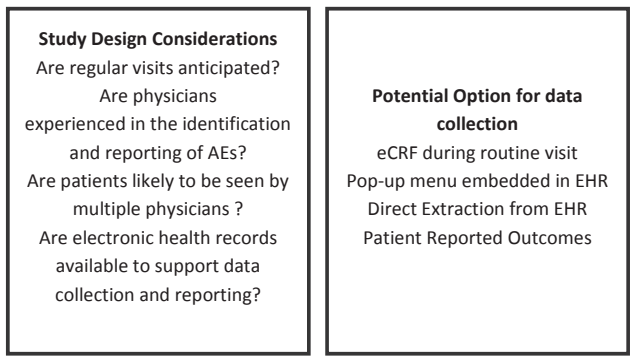

Fig. 2. Potential options for data collection. EHR, electronic health record.

and reporting information about an AE, as well as information about the relevant context such as comedication/comorbidities, will depend on (1) the objectives and design of the trial; (2) whether the patient is randomized to any treatment and whether those treatments are already licensed or not; (3) the normal treatment pathway of the patient in the country where the trial is being conducted (i.e., the regularity with which patients will routinely visit their treating physician or whether the patient routinely visits multiple physicians for different aspects of their health care); and (4) the availability of electronic health record (EHR) data or the use of case report forms for data collection and reporting. A variety of options are described below and summarized in Fig. 2.

When thinking about how to gather safety data in the absence of trial visits, where a marketed product is being used, it may be attractive to consider the use of the spontaneous reporting systems that are in place in many countries. These systems have been put in place to enable patients and physicians to report AEs that they believe are associated with a drug [10,11] directly to their local authorities. The advantage of this type of approach is that the market authorization holder can continually monitor the systems for any reported events as part of their standard pharmacovigilance activities. However, spontaneous reporting systems are not designed to and do not support reporting for a trial as the source of data cannot be traced, and information of the event is often incomplete. This may lead to problems with assigning relatedness to the medicines. Often, there is no scope within the systems to (re-)evaluate the relatedness of ADRs submitted by patients or physicians to drug exposure or to specifically label potential events as AEs instead of ADRs. Furthermore, there is known underreporting of events for medicines with which patients and physicians are familiar. In general terms, therefore, spontaneous reporting systems support the detection of potential unknown ADRs; however, they are not suited for estimating the incidence of ADRs [10,12].

Patient-reported outcomes collected both via validated instruments and web-based sources are becoming increasingly important in understanding the benefits and risks of medicines in the real world. Indeed, numerous pharmacovigilance programs are already integrating structured patient reporting, with evidence of improved detection of treatment risks [13]. However, to be accepted by industry and regulators, there needs to be consensus on what and how data should be collected; how safety signals should be managed; and whether or not physician confirmation is appropriate when patient or carers are reporters.

EHRs are adopted by an increasing number of practices and hospitals and can therefore be instrumental in collection of information about specific AEs. To facilitate a more structured enquiry about symptoms, events, or other relevant information, electronic pop-up menus incorporated in the EHR system could be helpfuland indeed have been shown to support accurate reporting in pragmatic trials [6]. However, given the fact that EHR systems are developed to support patient care rather than clinical research, many systems are not validated for use in clinical research or meet the requirements of international safety reporting [14,15]. If EHR systems are to be used, it is important to discuss and understand how physicians enter information about potential AEs into the EHR system. Known ADRs are unlikely to be the sole reason for a patient to visit their physician, any detailed information about the event may only be captured as free text, and therefore, it is essential to ensure that the free text fields of the EHR system can be searched for information that is relevant for AE reporting to limit under reporting of these ADRs. On the other hand, an event that was not already known to be associated with the medication may actually be a reason for consulting the physician but may not be labeled as such. The level of missing data, misclassification of events, and potential lag between an event happening and the availability of data for expedited reporting are all aspects that will impact the suitability of EHRs systems for reporting events. For example, to depend on EHR surveillance fully, the EHR system needs to capture all physician encounters both within the trial setting and also any other settings where the patient may receive medical care. It must also capture all necessary data to support the reporting and interpretation of the event, such as the time to onset of event, a description of the event, seriousness criteria, drug relatedness, and the outcome of the event as well as drugs prescribed at time of event and information regarding related comorbidities.

The Salford Lung Studies have been designed to evaluate the effectiveness and safety of the once-daily combination of the ICS fluticasone furoate and the novel LABA vilanterol (VI) (Relvar) compared with existing maintenance therapy in a large, real-world population of patients with COPD [16] and asthma [17] in conditions of normal care. Both these studies were supported by an integrated primary and secondary EHR system which enabled physicians to monitor the occurrence of potential AEs in near real time. Data were reviewed daily by an independent trial safety team of physicians and nurses. If events were identified, the trial team contacted the treating physician to establish the relatedness of the event to the drug [16,17]. Such integrated systems offer the potential for near real-time safety reporting to the trial sponsor, which is comparable or even beyond that currently available in the routine clinical trial setting where non−serious events are generally collected at least every 4 weeks.

1.4. Monitoring of trial conduct

Regulatory agencies have stressed the need for pharmaceutical companies to develop more proportionate and risk-based methodologies for clinical trial monitoring [18,19], as the resource-intensive ‘‘traditional’’ approach to trial monitoring becomes less feasible as trial complexity

increases. This point of view corresponds to the current ICH GCP guidelines, which explicitly dictate that "the sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials" ([20], p.30).

Various risk assessment tools have been developed that can aid protocol developers in establishing the risk level of a trial by considering the wide range of possible sources of issues that may occur during the conduct of clinical trials. For example the procedures used in the ADAMON and OPTIMON studies [21,22] or TransCelerate's Risk Assessment Categorization Tool [23]. These tools may be useful for pragmatic trials as well, provided it is taken into account that the likelihood of risks occurring in a pragmatic trial or the impact may be different from a traditional trial. For example, failure to follow the protocol is often cited as being one of the top five deficiencies of efficacy trials when audits are conducted by regulatory authorities. In contrast, in a pragmatic trial, because the protocol should remain very flexible to reflect standard clinical practice, less protocol deviations may be expected. If pragmatic trial protocols request data collection that is not part of routine care but regarded as of key importance to the trial, the risk of missing data (which may be regarded a protocol deviation) may be higher in pragmatic than in traditional randomized controlled trials due to the generally less strict follow-up requirements and the participation of a higher proportion of research-naive physicians. Treatment adherence is likely to be much lower in a pragmatic trial and would be considered a risk in a traditional trial. However, lack of adherence may actually drive the real-world effectiveness or safety of the medicine and is therefore not a risk that would be actively managed in a pragmatic trial.

The main challenge when designing a monitoring plan for a pragmatic trial is defining how to manage each of these risks. For example, in a traditional trial, a site visit and retraining may be triggered if investigators continually fail to accurately complete the electronic case report form (eCRF) and/or report SAEs in a timely manner. In the case of a pragmatic trial, especially where data are being extracted directly from the EHR, some missing data are inevitable and should be factored into the protocol design and data analysis plans. Although large problems with missing data may trigger some (re-)training, one would be reticent with this as it may interfere with the real-world nature of

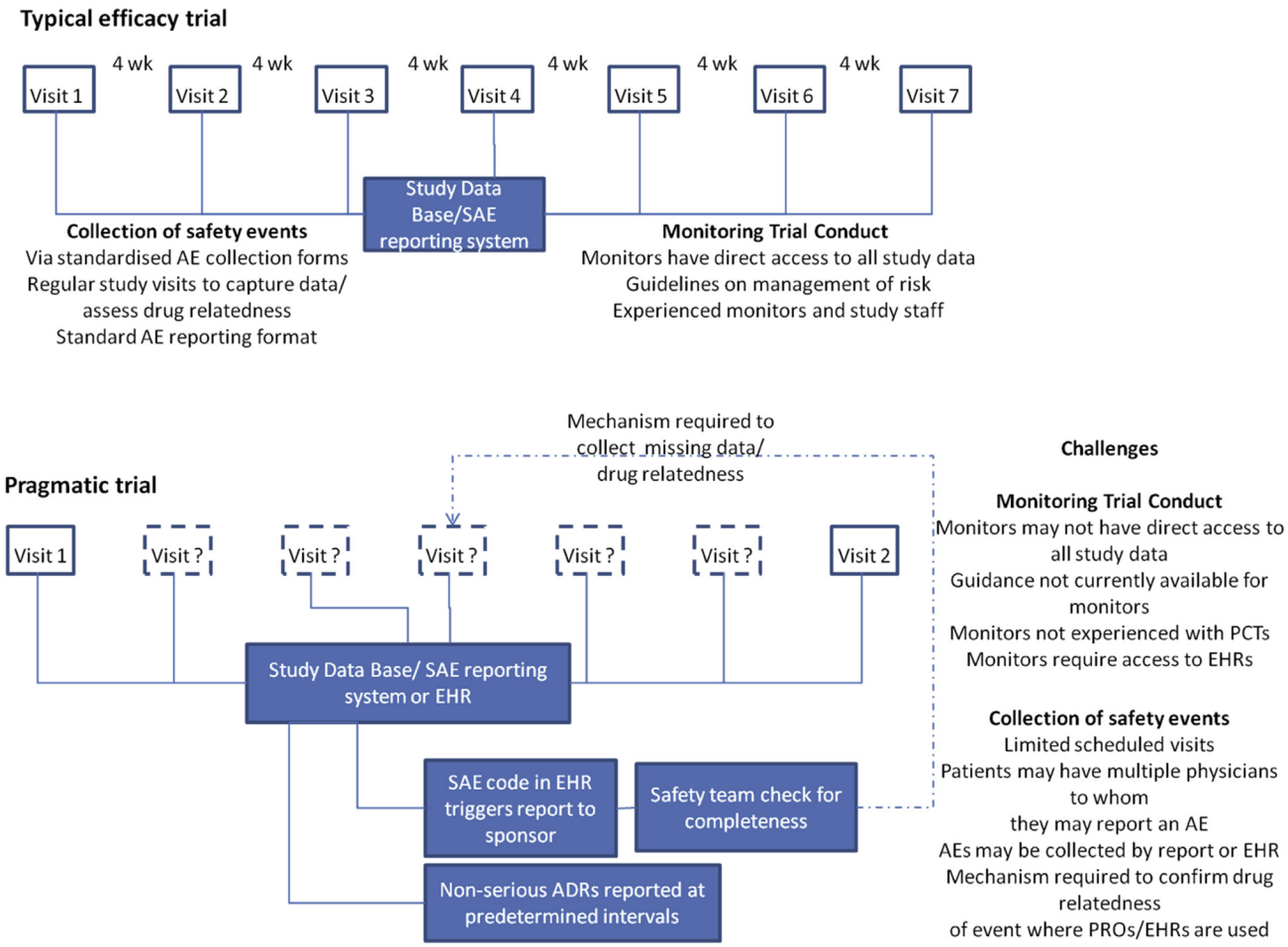

Fig. 3. Comparison between efficacy/safety and pragmatic trials. AE, adverse event; SAE, serious adverse event; EHR, electronic health record; ADR, adverse drug reaction; PCT, Pragmatic Clinical Trial; PRO, patient-reported outcome.

the study. The use of broader inclusion criteria, as is typical for pragmatic trials, may in fact result in less favorable risk assessments, as more vulnerable patients are included. The same may be true when including investigators that are less experienced. Each of these could trigger the requirement for additional site visits which may impact on routine care.

Various approaches to monitoring are being implemented, and central monitoring approaches are being more routinely adopted [24]. For instance, statistical monitoring may help in identifying unlikely or inconsistent data patterns (and may in that respect be preferred over on-site visits) [25]. Random and targeted source data verification (SDV) may reduce the volume of data that is to be SDV-ed by the clinical research assistant (CRA) [26–29]. Remote SDV may remove the need to visit trial sites physically [30,31]. The use of centrally available data allows for a dashboard-like overview of key performance indicators or metrics, which may be used to trigger on-site visits if specific thresholds are exceeded (see [23] for example). However, adopting centralized forms of monitoring that require regularly updated sources of data may be challenging in a pragmatic trial. Often investigators need to apply to access EHR records. Therefore, what data are required and how often it is required will in general have to be decided in the protocol design/site feasibility stage, to ensure access can be sought to allow trial recruitment, data completeness, and other trial performance metrics to be assessed.

In the case of on-site monitoring, it is important to ensure that the EHR systems can support requirement for monitoring with regard to controlled access (e.g., monitors should be given unique credentials to access only those records of patients enrolled in the study, and they should not be able to access other patients records who have not consented to be part of the study). As described above, this is often a challenge when working with EHR systems that have been developed to support patient care rather than clinical research.

In conclusion, the risk-based monitoring framework provides flexibility, which may benefit pragmatic trials, but also requires careful and early consideration of the monitoring plan for each individual trial which may be challenging.

2. Discussion and conclusion

ICH Guidelines, for all clinical trials in any phase, dictate that all SAEs must be reported to the sponsor and within 24 hours of the investigator becoming aware of an event unless directed otherwise in the protocol. In pragmatic trials, that generally follow routine clinical practice, additional study-related activities and follow-up visits should be minimized. This may complicate the structured collection of drug-related safety data. However, several different options for data collection are available to researchers depending on the study design which range from more traditional collection of safety data using an eCRF during routine care visits to the remote surveillance of EHR data.

The risk-based monitoring approaches being used to increase efficiency of monitoring trial conduct can be applied to pragmatic trials. However, although the types of risks associated with the implementation of a pragmatic trial are similar, their relative importance, detail, and/or interpretation are likely to be different from a traditional trial. Remote monitoring techniques currently rely on data being fed through companies' data management systems; this works well where data collection is done via eCRF, however, where data are collected directly from an EHR system a mechanism will need to be put in place to allow monitors to access the data required. This requires up front planning and discussion with data system custodians as it is possible that investigators may need to apply for permission to access the data (even remotely) at set intervals throughout the study.

Whatever approach is taken for collecting safety data and monitoring trial conduct, in a pragmatic trial, it is likely to be ''nonstandard'' compared to an explanatory trial (Fig. 3) and will therefore require early and detailed discussions with ethics review boards and regulatory authorities in all participating countries.

Acknowledgments

The authors extend their thanks to Dr Susan Collier for her careful and constructive critique of the manuscript. The work leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007/2013), and EFPIA companies' in kind contribution. The research leading to these results was conducted as part of the GetReal consortium and included literature review and interviews with stakeholders from academia, research institutions, contract research organizations, pharmaceutical industry, regulatory authorities, health care insurers, health technology assessment (HTA) agencies, general practitioners, and patient organizations. For further information please refer to http://www.imi-getreal.eu/http://www.imi-getreal.eu/http://www.imi-getreal.eu/http://www.imi-getreal.eu/.

References

[1] Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel GJMW, Grobbee DE. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. J Clin Epidemiol 2017;88:7–13.

[2] Rengerink KO, Kalkman S, Collier S, Ciaglia A, Worsley SD, Lightbourne A, et al. Series: Pragmatic trials and real world evidence: Paper 3. Patient selection challenges and consequences. J Clin Epidemiol 2017;89:173–80.

[3] Worsley SD, Rengerink KO, Irving E, Lejeune S, Mol K, Collier S, et al. Series: Pragmatic trials and real world evidence: Paper 2. Setting, sites, and investigator selection. J Clin Epidemiol 2017;88:14−20.
[4] European Trial Directive 2001/20/EC. Available at. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf. Accessed September 20, 2016.
[5] Konstantinou GN. Pragmatic trials: how to adjust for the 'Hawthorne effect'? Thorax 2012;67:562.
[6] van Staa TP, Dyson L, McCann G, Padmanabhan S, Belatri R, Goldacre B, et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials. Health Technol Assess 2014;18:1−146.
[7] Regulation (EU) No 536/2014 of The European Parliament and of the Council. Available at. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Accessed September 20, 2016.
[8] Guideline for good clinical practice E6(R2). Available at. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191488.pdf. Accessed September 20, 2016.
[9] MRC/DH/MHRA Joint Project. Risk-adapted approaches to the management of clinical trials of investigational medicinal products 2011. Available at http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf. Accessed September 20, 2016.
[10] McLernon DJ, Bond CM, Hannaford PC, Watson MC, Lee AJ, Hazell L, et al, Yellow Card Collaboration. Adverse drug reaction reporting in the UK: a retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. Drug Saf 2010;33:775−88.
[11] de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K. Adverse drug reaction reporting by patients in The Netherlands: three years of experience. Drug Saf 2008;31:515−24.
[12] Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The weber effect and the United States Food and drug Administration's adverse event reporting system (FAERS): analysis of Sixty-two drugs Approved from 2006 to 2010. Drug Saf 2014;37:283−94.
[13] Banerjee A, Ingate S. Web-based patient-reported outcomes in drug safety and risk management: challenges and opportunities? Drug Saf 2012;35:437−46.
[14] Electronic health records MHRA position statement. Available at. http://forums.mhra.gov.uk/showthread.php?1885-Electronic-Health-Records-MHRA-Position-Statement. Accessed September 20, 2016.
[15] Meineck A-K, Welsing P, Kafatos G, Burke D, Trelle S, Kubin M. Series: Pragmatic trials and real world evidence: Paper 8. Data collection and management. J Clin Epidemiol 2017;91:13−22.
[16] Bakerly ND, Woodcock A, New JP, Gibson JM, Wu W, Leather D, et al. The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease. Respir Res 2015;16:101.
[17] Woodcock A, Bakerly ND, New JP, Gibson JM, Wu W, Vestbo J, et al. The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in asthma. BMC Pulm Med 2015;15:160.
[18] FDA. Oversight of clinical investigations —A risk-based approach to monitoring 2013. Available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf. Accessed September 20, 2016.
[19] EMA. Reflection paper on risk based quality management in clinical trials 2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf. Accessed September 20, 2016.
[20] ICH GCP. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2) 2015. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf. Accessed September 20, 2016.
[21] Brosteanu O, Houben P, Ihrig K, Ohmann C, Paulus U, Pfistner B, et al. Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials. Clin Trials 2009;6:585−96.
[22] Chêne G, Alberti C, Bellissant E, Bénichou J, Carrat F, Chatellier G, et al. Evaluation of the efficacy and cost of two monitoring strategies for public clinical research. OPTIMON trial: OPTImisation of MONitoring of clinical research studies [protocol not published]. Eval efficacy cost two Monit Strateg Public Clin Res 2008. Available at https://ssl2.isped.u-bordeaux2.fr/OPTIMON/default.aspx. Accessed September 20, 2016.
[23] Position Paper Risk Based monitoring. Transcelerate 2013. Available at http://www.transceleratebiopharmainc.com/wp-content/uploads/2013/10/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf. Accessed September 20, 2016.
[24] Morrison BW, Cochran CJ, White JG, Harley J, Kleppinger CF, Liu A, et al. Monitoring the quality of conduct of clinical trials: a survey of current practices. Clin Trials 2011;8:342−9.
[25] Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. Clin Trials 2008;5:49.
[26] Getz K. Low hanging fruit in the fight against inefficiency: Direction from regulatory agencies would help eradicate wasteful 100 percent source data verification. Appl Clin Trials 2011;20:30.
[27] Hines S. Targeting Source Document Verification: targeted SDV provides data validation by comparing trial data with primary health records. Appl Clin Trials 2011.
[28] Grieve AP. Source data verification by statistical Sampling: issues in implementation. Drug Inf J 2012;46:368.
[29] Tantsyura V, Grimes I, Mitchel J, Fendt K, Sirichenko S, Waters J, et al. Risk-based source data verification approaches: pros and cons. Drug Inf J 2010;44:745−56.
[30] Radovich & Frick Remote Source Document Verification (rSDV) A sponsor perspective and results of implementation. Available at. http://www.pharmavigilant.com/uploadDocs/1/December-Monitor-article-on-rSDV.pdf. Accessed September 20, 2016.
[31] Uren SC, Kirkman MB, Dalton BS, Zalcberg JR. Reducing clinical trial monitoring resource allocation and costs through remote access to electronic medical records. J Oncol Pract 2013;9:e13−6.