Towards Improved Clinical Trial Monitoring

Introduction

Although more drugs are being approved in recent years (1), cardiovascular disease drugs together with oncology drugs are still lagging (2). Based on the lead indication (i.e. the indication the drug will be developed for), cardiovascular drugs have the lowest likelihood of approval with 8.7% of the drugs that enter clinical development being approved (2). In addition, medical devices, of which a large proportion is intended for cardiovascular diseases, are dependent on clinical development in order to get market approval (3,4). TABLE 1 shows the distribution of different types of clinical trials in the cardiovascular realm. These data highlight the importance of high-quality research within the cardiovascular disease area to ensure the clinical development of cardiovascular drugs, devices, and best treatment practices.

Clinical trial monitoring is an important quality control measure, which contributes to high-quality research (5,6). Nahm *et al* have illustrated the essential role of clinical trial monitoring since the average error rate identified by source data verification was 976/10,000 data points (7). This study suggests that medical record transcription is error-prone and correlates with other operational problems that need to be addressed by a monitor (7). Clinical trial monitoring can address underlying operational problems by identifying root causes, clarifying confusion about the protocol, improving protocol and Good Clinical Practice (GCP) compliance, and by improving communication between investigators and project coordinators (8). Overall, clinical trial monitoring focuses on high-quality research by ensuring protocol compliance (8,9).

Table 1. WMO-obligatory trials in the Netherlands and FDA/EMA approvals 2019.

WMO	n/cardiovascular trials	n cardiovascular/total FDA approvals 2019	n cardiovascular/total EMA approvals 2019
Drug	140/297 (47%)	4/48 (8.3%)	2/30 (6.7%)
Medical device	104/297 (35%)	16/47 (34%)	NA
Other intervention	53/297 (18%)	NA	NA

Refs: 3, 9, 10. WMO = Medical Research Involving Human Subjects Act in the Netherlands.

Research objective and questions

Diagram B.V. aims to acquire the highest quality of monitoring within the available budget of a clinical trial. Specifically, Diagram B.V. desires to know how they can provide guidance to research teams so that the teams know what is expected from them and are able to perform high-quality research. The aim of this research project is to identify whether the information provision and communication of Diagram through the monitoring process can be improved, by providing insights into the experiences of investigators involved in Diagram's monitoring process. The following main research question was formulated:

- How can the information provision and communication through the monitoring process of Diagram be improved?

And the accompanying sub-research questions:

1. What factors are important for protocol familiarization and compliance?
2. What factors impact protocol acceptance by the site study teams?
3. What external factors impact protocol compliance behavior of site study teams?

Methods

To answer the research questions, qualitative research methods were used, since these allow for an in-depth understanding of the opinions, perspectives, experiences, attitudes, processes, and suggestions of the respondents (11). Semi-structured interviews with site study staff allowed for triangulation between study coordinator, sub-Principal Investigators (PI), and research nurses. Data analysis was performed using QDA miner Lite. Both structured (i.e. based on available theory) and open coding (i.e. extracting concepts/topics from the data) were applied.

Results

During this research project, 17 respondents were interviewed: seven research coordinators, seven research nurses and three sub-PIs. Here we highlight the key findings of this research project. The results are structured based on the sub-research questions. **Box 1** displays the key findings regarding the provided information through the monitoring process of Diagram B.V., and the knowledge that impacts protocol compliance. **Box 2** presents the most important perspectives of clinical research professionals regarding the provided information. In addition, facilitators and barriers that impact protocol and study acceptance (e.g. motivation to conduct clinical trials, agreement with the communication with Diagram) were assessed. The most frequently mentioned external factors that hamper clinical trial conduct were organizational (**Box 3**).

Respondents indicated that a CRO/sponsor could address these organizational barriers by:

1. Emphasizing that quality data is required (for example during an initiation visit)
2. Communicating responsibilities clearly
3. Scheduling (online) meetings with the involved discipline
4. Communicating directly with the involved departments

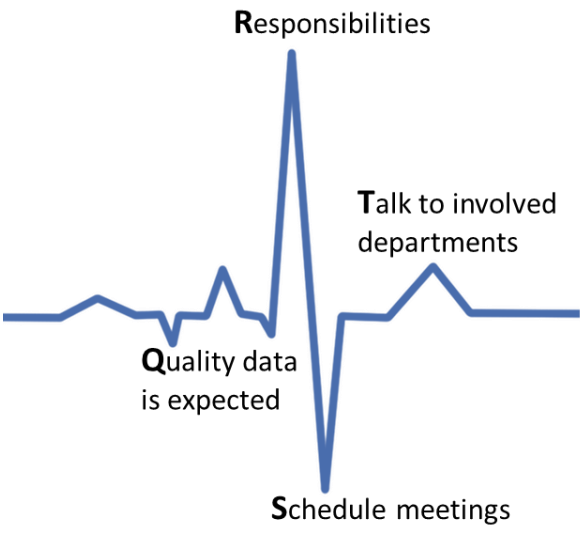


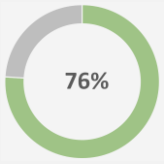
Figure 3. How a CRO can confront organizational problems.

Box 1. Main research findings – knowledge

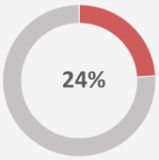
- Research coordinators require information on

- The protocol, PIF and CRF educate the research sites on the new study
- Inclusions rates elicit honest competition and provide insight in the study progress
- Newsletters ideally include information on common errors and how to deal with them in agreement with the protocol
- Clinical study reports are not always provided. Respondents suggested to include a summary in lay language

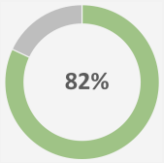
Box 2. Main research findings – attitudes



Respondents suggested that the outcome expectancy based on the provided information is sufficient.



Respondents mentioned that engaging different stakeholders during the design eCRF increases its practicality.



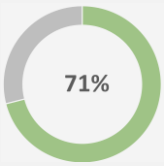
Most respondents would like to receive an eCRF (1 month) before the initiation visit.

2/3 sub-PI's implied that monitor requirements not always clear (e.g. on source documentation).

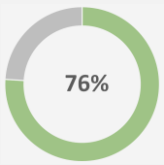
Several respondents would like to discuss the trajectory that 1 patient undergoes during trial to identify logistical issues.

Various respondents mentioned that a frequent change of monitor is annoying.

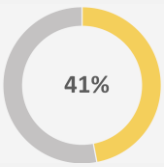
The clinical trial monitor should be pragmatic and have a feeling for the clinical reality according to the respondents.



Most interviewees advocated that the first monitor visit should take place after first inclusion(s) (100% SDV).



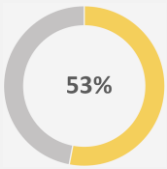
Most respondents are motivated by inclusion rates (and honest competition).



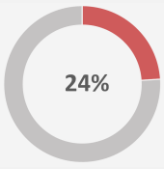
Clinical research professionals are intrinsically motivated to help patients.

The percentages should be interpreted tentatively. Because qualitative methods were applied, the percentages do not necessarily reflect the proportion of the clinical research professionals that agrees with the statement. Rather, the percentage indicates how many respondents spontaneously mentioned the issue/statement.

Box 3. Main research findings – external factors

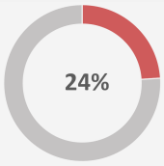


Most respondents encounter difficulties when working together different disciplines.



A difficult study population; very specific eligibility criteria, may hamper study progress.

There is a lack of study-minded hospital personnel according to different respondents.



Several respondents indicated that there is a lack of commitment of the physicians.

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Conclusions and recommendations

- Providing the CRF before the initiation could contribute to a better understanding of the clinical trial protocol.
- Especially when different disciplines are involved it is vital to discuss responsibilities and gauge difficulties in order to circumvent (logistical) problems later.
- In order to comply to the protocol, an intuitive and user-friendly eCRF should be in place.
- The first monitor visit should take place as soon as the first patient is included. This finding is in accordance with Knatterud *et al* who recommended that site visits take place after the first patient is included so that errors (e.g. in the eCRF) can be detected early (12).

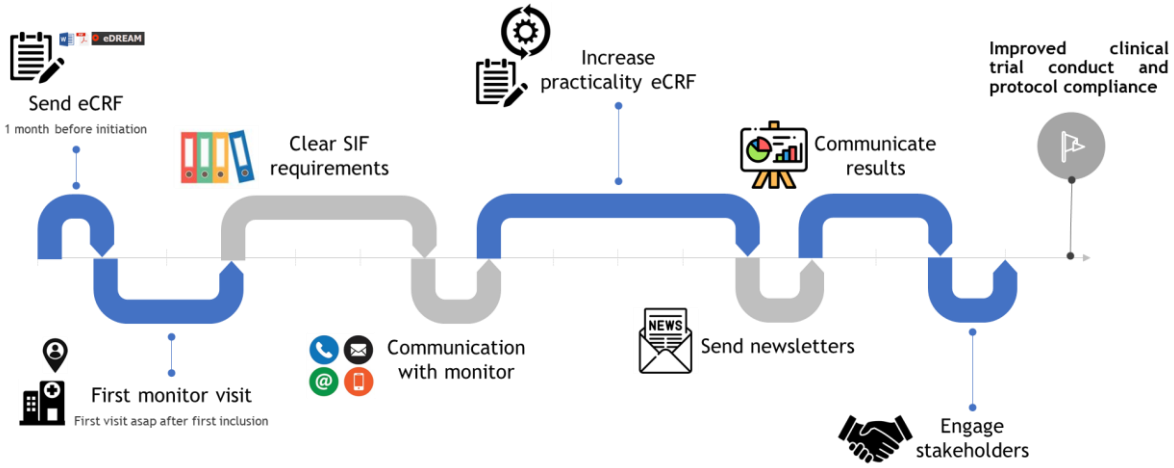

Figure 4. Recommendations to Diagram to improve protocol compliance by means of the clinical trial monitoring process.

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