PharmaSUG China 2021 - Paper 16

Quality Management of Critical Data from eDevice in Decentralized Clinical Trial

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ABSTRACT

With emerging technical innovations, clinical trial site level activities are no longer restricted within research sites. Instead, participants or patients have more autonomy and voice in how and where to conduct trial assessments. The concept of decentralization is then introduced and reflected on the notion of participant – directed process. Decentralized clinical trials, providing numerous advantages over traditional ones, have won great recognition, especially under global pandemic of COVID-19. However, in accompany with such concepts, one of the challenges to clinical researchers is to collect, monitor, and analyze data with high diversity. In BI, we conducted several trials either partially or completely remote. In this setting, we have encountered some problems during study design, and implementation. For example, when previous target data is not complete in time, how we can assign subsequent drug dose correctly; when the key data reported from user-end device is not reliable, how to control measurement error; and how to mitigate other emergent data issues brought by complex decentralized trial design. These challenges have not been evaluated and discussed widely and carefully in pharmaceutical industry. In this paper, we take ulcerative colitis studies as examples to discuss how we overcame the challenges above and explore the potential improvements in future trials.

INTRODUCTION

Clinical trial, as one of the most recognized research tools to evaluate new treatment and therapy, has been the golden standard in drug development. Trial participants are usually asked to visit research sites as scheduled, and to receive study treatment and measurements, from both safety and efficacy aspects, under the instruction of site staffs. Site would then collect and document all data points according to the pre-defined eCRF, and transfer to sponsor for further analysis. The above execution mode places quite strict demands not only to research site staffs, but also to participants, especially if the target study population are those with acute disease occurrence. Onsite clinical visit is time and resource consuming, and patients are heavily tied to sites, which could be interrupted due to many reasons, for instance, the global pandemic of Covid-19 had pressed the pause key for almost all clinical studies at the site level[1].

Decentralized clinical trial (DCT), is introduced as a new form of method that to conduct study without physical restriction of clinical research sites. However, DCTs do not mean to completely disrupt the connection between participants and clinical sites. Instead, participants can show up at sites for a couple of visits (mainly for drug administrations), and to complete the rest of study assessments at home via digital technologies. The magnitude of decentralization is inversely influenced by how close the study operations are tied with sites[2]. Clinical data collection turns out to be a combination of both site-based and virtual. Such new concept provides more flexibility to participants, especially if their physical conditions are not suitable for onsite visits. Conversely, it raises more challenges on data collection and management since data collected without instruction by healthcare professionals would need more attention, to better serve further analysis.

Data from electronics was quite new to trial team, and the responsibility was not clearly defined at the beginning. Colleagues with limited experience in dealing with eDiaries would take for grant to treat data similar as from central lab. Lack of awareness of extra data cleaning work has led to messy situations in trial team when assigning follow up treatment. Programming team was then involved due to extremely complex calculation and struggling with data check. In next section, we would discuss the challenges we confronted and how we dealt with in ulcerative colitis (UC) studies.

MAYO SCORE AND EDIARIES

As a part of the decentralized data collection mentioned above, Electronic Patient Diaries System (eDiaries), a digital data entry system for daily patient-reported outcomes data from patients' end, is widely employed in UC trials[3, 4]. FDA also highly recommends sponsors to propose electronic data collection, as an alternative to paper copy, since eDiary is a traceable data source to check changes[5].

To evaluate disease activity and treatment efficacy among UC patients, we use Mayo Score calculation as the basis for primary clinical endpoint. Mayo score is a scoring system with four components: stool frequency, rectal bleeding, mucosal appearance at endoscopy, and physician rating of disease activity. Endoscopy and physician rating should be done at site visits and evaluated by clinicians due to the property of assessments, while stool frequency and rectal bleeding should be daily reported by patients (Figure 1). Any decreasing in stool frequency or no blood detected in stool would indicate the sign of disease improvement or remission, vice versa. The accuracy and completeness of these two efficacy measurements would result in valid assessment of clinical endpoint. We collaborated with a vender to conduct this remote data collection. The vendor provided handheld device to patients to collect daily diary data, and tablet onsite to collect physician assessment and provide report to investigators for disease overview. The complicated algorithm for mayo score calculation was pre-specified in the system, and vendor side would also clean data via data change request (DCR) raised by site staff, and prepare acceptable SDTM dataset.

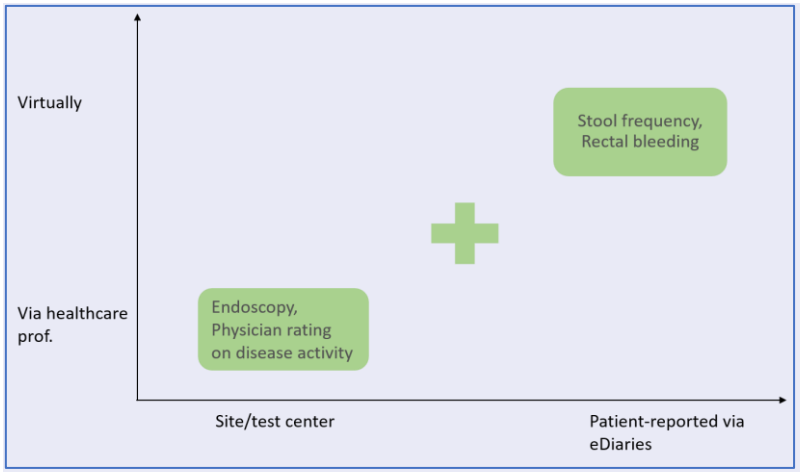

Figure 1, Mayo score data collection

Investigators were trained to enter physician global assessment (PGA) and date into a trial tablet device. The vendor would then calculate relevant mayo scores to help evaluation based on pre-defined algorithm. It was aimed to achieve real time data receiving and feedback to physician for the next step treatment. Nevertheless, data report from vendor's system was not consistent with later comparison report checked by programming team. For example, date manually entered via vendor side was not the same with the one collected in eCRF, which was critical for daily diary data selection and mayo score calculation. Such discrepancy would affect not only treatment regimen, but also the trial conduct in the next step. There are quite a lot discussions between trial team and vendor team to figure out the reason of inconsistency, including contact sites and patients for clarifications. Unfortunately, the data correction from vendor's system was independent from usual query process (Figure 2). The data change request needs to be raised by site and then to be updated by vendor side, which usually took several rounds for issue clarification and data correction. Under such circumstance, our clinical programming team took over all data check and validation work.

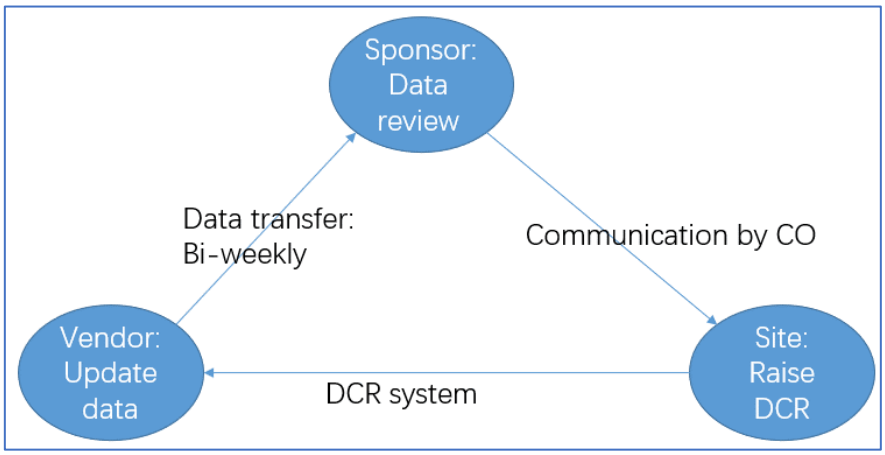

Figure 2, Mayo score data cleaning flow

On top of the challenge we met, considering the property of the investigative disease treatment regimen would be decided based on previous performance of efficacy measurements. Site physicians would evaluate if overall disease activity is stable or worse, then to decide if patients need to take higher dose of study drug or rescue mediation to treat disease flare (relapse)., Or patient is in good status to stay with maintenance treatment. However, if decentralized data from vendor could not be available in time, or is not ready to merge with sites' data, neither sponsors nor investigators could make judgement on the correct treatment and send medication kits to sites. After clinical programming team receiving the data from our vendor, we've detected several patients that were not assigned to the correct treatment arm. For example, patient reported worsening of symptoms(increased stool frequency or lasting rectal bleeding) into eDiaries, but these data were not cleaned by vendor at that time point, and thus investigator wrongly assigned patients to lower dose arm, which placed patients under risk and led to important protocol deviations.

Besides, we've found patients could forget to report data, report wrong data, and mistakenly restore edevice to default settings, or edevice ran out of battery. These measurement errors would cause the incorrect derivation for efficacy endpoint and bias trial results. Meanwhile, these data quality issue also revealed the insufficient training to patients, and we were not able to monitor patients under ideal conditions. With the outbreak of COVID-19 pandemic, these issues have led to a much acute question. Since some research sites and test centers were closed or patients refused to go to sites, they would have very limited assessments of safety or efficacy. Then eDiaries would be the only available data source during such period. Having plausible data turned to be particularly important to assess what was going on of our patients.

To deal with the above data issues, programming team had spent quite a lot efforts to develop codes for data check with high frequency. When under time pressure for interim analysis, we conducted biweekly data comparison between internal calculation and results from vendor, and marked all suspicious cases for team's review. All efficacy endpoints were re-derived from source data including daily diary and clinician reported outcomes, based on aligned algorithm to avoid any held back from vendor's system. The data correction process was quite slow considering the difficulty for site staff to raise request, especially during the pandemic, or the communication between sites and vendor was not clear.

CONCLUSION

The trend of new technologies in clinical data collection is inexorable. Clinicians can evaluate patients' facial expression via mobile apps in psychology trials; real-time electrocardiogram data can be uploaded to server via wearable device. These advanced technologies explore and enlarge the possibility of reaching out to patients under various scenarios. At the same time, the potential complexity should never be ignored or overlooked. When decentralized data collection is co-related with the following treatment assignment, data comparison between vendor and internal trial team is essentially critical. Programming should be involved in early stage and align the overall system algorithm set up with vendor together. Once any held back occurred either from sites or from eDiaries, appropriate team members or experts should be able to take over and support decision making. Meanwhile, it is recommended to avoid unnecessary manual duplicated data entry via third-party eDevice in the design stage. Any data scenario should be fully considered with backup plan to make sure timely data correction. Internal data check should be planned ahead of trial conduction, and to test if complexed design involving treatment assignment can be accommodated based on data from eDevice.

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