Biostatistical and Regulatory Considerations for Dermatology Trials

Highlights:

- While the EMA and FDA released guidance documents on trials during the pandemic, statistical considerations were overlooked initially; the first guidance documents focused primarily on safety for trial participants.
- Recently updated guidance includes much more on data reporting requirements.
- There are key considerations around data reporting/CRFs for dermatology clinical trials that must be noted as a result of COVID-19.
- It's critical to ensure risk assessment includes a statistical review.

Impact on Data Reporting

Although the EMA and FDA very quickly released guidance documents on conducting clinical trials when the pandemic's disruptive impact became apparent in the spring of 2020, statistical considerations were given limited attention. In June 2020, a statistical considerations update was released, addressing data reporting from a statistical perspective at length.

Protocol deviation reporting makes it difficult for study statisticians and programmers to pull out COVID-19 related deviations if reported in text format and include them in a summary table, but it's important to continue reporting protocol deviations related to COVID-19, nevertheless.

Because the FDA is interested in knowing COVID's impact at both the study and the subject level, it's important to note distinct information in the CRF.

COVID-19 impact on data reporting:

- Missed visits/delayed visits (out of window)
- Impact on dosing (site level, trial participant level, supplier level)
- Discontinuations due to COVID-19 (subject level and site level)
- Use of alternative or rescue treatments (due to COVID-19)
- AEs related to COVID-19
- Missed endpoint evaluations/use of alternative methods of endpoint evaluations

Additional factors that contribute to the impact on data reporting should be noted as well, such as telemedicine in place of clinic visits or efficacy assessments from photographs taken by subjects.

Risk Assessment

Every study needs to go through a risk assessment, which should be reviewed multiple times during study conduct, and it's important now, more than ever, to make sure the risk assessment includes a statistical review.

Though the sponsor can be informed of potential concerns that may negatively impact the endpoint analyses during the study, one particular area of focus should be the amount of missing data. For example, how much missing data is there and why is it missing? If it's because the sites are not entering the data in a timely manner, for example, this should be addressed immediately.

Missing data is one of the biggest concerns in any study, whether it's a Phase II study that will power your pivotal studies or if it's your pivotal studies themselves where trial success is dependent on demonstrating statistical significance between your active treatment and placebo. And the risk assessment should also anticipate dealing with closures during COVID-19. If a site is closing because they have resource issues due to COVID-19, for example, is it possible that subjects at the site can be moved to another site? If this is a possibility, how will this impact data reporting? It may be that there is a different investigator who most likely didn't assess the subject at the baseline visit but will now be assessing the subject at the endpoint. Will your EDC system support this? And can changing investigators during the study have an impact on the efficacy reporting?

It's important for your risk assessment plan to cover all of this – and to have a plan for these contingencies as early on in your studies as possible. For the duration of the pandemic, it's recommended that you include data review meetings using a DMC or DSMB.

As the risk assessments are being reviewed during the study, the SAP should be updated to add any additional analyses that you will want to support your study. For example, you may add a sensitivity analysis adding subjects to the PP population if their only deviation related to out of visit windows at endpoint related to COVID. Alternatively, you may want to add a modified per-protocol population to include these subjects and run the analyses for both the per-protocol and modified per-protocol populations.

Efficacy Considerations

But before this decision is made, it needs to be assessed from a clinical standpoint as well. For example, consideration may be given as to the impact on efficacy from increased dosing past endpoint or if the subject was only given enough medication to dose until the expected time of the end-of-treatment visit but came in late for the endpoint evaluation. In that case, you know there is a potential loss of efficacy and you may not want to consider a modified per-protocol population to extend the dosing window. Your risk assessment will need to take these types of events under consideration.

The pandemic's impact on trials this year will undoubtedly continue to be felt moving forward. If you have any questions about your dermatology trials, please reach out to us.

About Synteract

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