

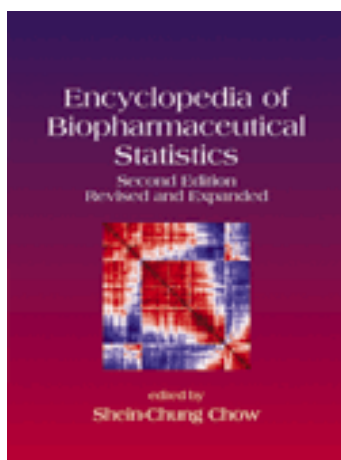
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Integrated Summary Report

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INTRODUCTION

There are many reasons to integrate and to summarize all the data from a clinical trial program. Each clinical trial in the program is unique in its objective and design. Some are small safety studies among normal volunteers, while others are efficacy trials in a large patient population. The primary reason to create an integrated summary is to compare and to contrast all the various study results and to arrive at one consolidated review of the benefit/risk profile. A second and important reason is to reach a defensible statistical conclusion, through an exploration of the integrated data, that no competing alternative hypothesis that can reasonably account for the observed findings exists. Third, pooling the data from various studies enables the examination of trends in rare subgroups of patients, such as the elderly, those with differing disease states (mild vs. severe), and those with comorbidities at baseline. Last, providing such a summary in the new drug application is required by the Food and Drug Administration (FDA) and other international authorities.

OVERVIEW

An integrated summary report is a compilation of all the evidence for efficacy and safety from the data collected in all completed clinical trials. There are two integrated summary reports: the integrated summary of efficacy (ISE) and the integrated summary of safety (ISS). Both are required for all new drug applications in the United States.

The analysis approach for the ISE is substantially different from that for the ISS. The ISS summarizes all data collected from the clinical trial program, including normal volunteers and patients. The ISE includes data only from those clinical trials that present some evidence of efficacy, either through surrogate markers or through well-designed tests for efficacy. The ISE requires a more prospective approach to analysis, whereas the ISS approach is more sensitive because it allows a retrospective search through all the data to expose possibly rare but important side effects. As a result, pooling data across studies is required in the ISS to obtain more reliable estimates of the incidence of rare adverse events. A pooled analysis in the ISE is not required, but it can be

useful for estimating a more precise treatment effect. However, pooling is generally not useful for substantiating evidence of efficacy, without side-by-side study results each showing evidence of efficacy separately. Therefore this entry has two sections. The first section is devoted to the ISE, the second pertains to the ISS.

There are a number of areas of specific interest that arise within the integrated summary report. A description of the demographic and baseline clinical features of the population treated during the course of the clinical trial program is necessary. Key questions concerning efficacy need to be addressed by considering the results of relevant trials and by highlighting the degree to which they reinforce or contradict each other. For example, when is it useful to pool trials to obtain a more precise estimate of the treatment effect? All the safety information available from the entire database of all studies should be summarized. How can the data be thoroughly searched so that any potential safety concern is identified?^[1]

INTEGRATED SUMMARY OF EFFICACY

Dose Rationale

One of the most important sections of the ISE is that on dose selection. Efficacy information at all doses studied should be analyzed in such a way that a dose or dosing interval can be recommended. Information that is needed to support a new drug application should identify an appropriate starting dose, as well as how to adjust dosage to the needs of a particular patient.^[1] The maximum dosage beyond which there is no likely benefit or that would produce unacceptable side effects should also be identified. It is important to identify the lowest dose exhibiting a clinically important effect. To know for certain that one has identified the minimally effective dose, it is often necessary to study a dose that has no clinical benefit compared to placebo. This section of the ISE should contain the information from the dose response studies, that is, controlled information on the minimum, maximum, and average dose from the response curve for efficacy. It should also contain any other information from other doses. Safety needs to be brought into the discussion because choosing the dose is always a risk/benefit decision.



In order to provide proper dose–response information, there should be at least one prospective dose–response study in the ISE that explores more than three doses. In principle, being able to detect a statistically significant difference using pairwise comparisons between doses is not necessary in such a trial, if a statistically significant trend (upward slope) across doses can be established using all doses. The more doses explored in this study, the better the dose–response curve will be characterized. It should be demonstrated, however, that the dose to be recommended has a statistically significant and clinically meaningful effect. This can be done in the dose–response trials or in other adequate and well-controlled trials.

The entire database should be examined extensively for possible dose–response effects. Limitations of study design should be considered. For example, the titration scheme designs should not be pooled with fixed-dose designs. Many trials will titrate to the desired response. Weaker responders would then receive the higher doses. This may lead to an inverted U-shaped dose–response curve. Despite the different designs, all clinical data should be examined for dose–response information.

The entire database should be examined to explore possible differences in subgroups of patients based on baseline differences. Age, gender, and race should always be examined. Other important covariates may be baseline disease severity and baseline comorbidities. Height, weight, renal function, and lean body mass are important in looking at the dose–response data as a function of body size and metabolism.

Efficacy Data

The International Conference on Harmonization guideline^[2] says that individual clinical trials to demonstrate efficacy must be performed and must be large enough to satisfy their objectives. Additional valuable information may also be gained by summarizing a series of clinical trials that address essentially identical key efficacy questions. This can be done in the ISE. The main results

of such a set of studies should be presented in an identical form to permit comparison across studies, focusing on estimates plus confidence limits. The use of meta-analysis to combine these estimates of treatment effect across studies of the same dose regimen is often useful because it allows a more precise overall estimate of the treatment effect at those doses. However, only under exceptional circumstances would a meta-analysis be the most appropriate way to demonstrate efficacy via an overall hypothesis test.

Fig. 1 shows the clinical trials that are summarized in the ISE. In this program, Phase IIB and Phase III studies are the focus of the ISE. These studies should be planned while taking into account that they will be combined and presented together for an overall estimate of the benefit of the therapy. They should have similar endpoints (primary and secondary), similar populations, and some overlap in the dose regimens. Phase IIB is the study that demonstrates “proof of principle,” usually through a statistically significant increase in efficacy with an increase in dose. There should be two Phase III studies—one to demonstrate a statistically significant and clinically meaningful benefit, and the other to replicate that demonstration.

Meta-Analysis

In pharmaceutical development, it is known at the time of positive Phase II results that a new drug application is likely to be filed. It is at this time that the researchers should start planning for the ISE. In the planning of the adequate and well-controlled trials, one should incorporate any needs that the ISE plan may require. It is at this time that the decision to do meta-analyses should be made in a prospective manner. The individual studies can then be designed with pooling as a goal. Which studies will be pooled and which studies will not can be decided prior to obtaining the results. Then pooling will not be influenced by the results. The decision to undertake a meta-analysis after the data from all the efficacy studies have been

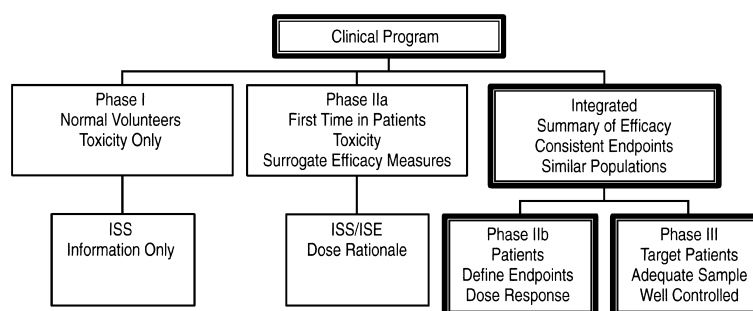


Fig. 1 The integration of efficacy information to support a marketing application.



reviewed cannot be made to save any negative or borderline results that were obtained in the individual studies. In such a case, the researchers could pick and choose studies so that the results favor the treatment being proposed. A simple principle is to perform a meta-analysis in a manner that is consistent with the conduct of a single well-designed randomized clinical trial.^[3]

Flather et al.^[4] address why we do meta-analysis: "Even large randomized clinical trials may not answer specific questions reliably because of weaknesses in their design or, more commonly, because they are not large enough to detect the moderate but medically important treatment effects that can be expected realistically." The primary reason for performing meta-analysis is to obtain more reliable estimates of the treatment effects. Secondary reasons for performing meta-analysis are 1) to summarize formally the available information on a particular treatment, and 2) to generate hypotheses that may be tested in future trials. For example, in the development of a treatment for ischemic stroke, each individual study could be powered for functional status, while the meta-analysis could be powered for mortality (which would generally take larger numbers). In this case, the randomized controlled trials are powered for differences in endpoints that are more sensitive (possibly, surrogates), while meta-analysis is powered for the less sensitive clinical endpoints. The pooling may allow the detection of clinically significant changes on clinical endpoints because of the increase in sample size. This is similar to the optimal information size discussed in Pogue and Yusuf.^[5]

In pooled analysis, all appropriate clinical trials should be included to avoid bias. Studies should be excluded if not of a consistent, similar design eligibility criteria, trial treatment regimens, concomitant medications, definitions of outcome events, or length of follow-up. Studies with incongruent results should not be pooled but should be examined for an explanation of their differences. Given the retrospective nature of most meta-analyses and the multiple comparisons that are carried out, many researchers believe that a *p* value of 0.05 is not stringent enough. Levels of 0.01 or even 0.001 should be routinely considered.^[6]

After the decision to do Phase III studies, develop a prospective protocol for your meta-analysis by defining specific hypotheses (primary and secondary) to be tested:

- Frame a question that is medically relevant and biologically sensible.
- Define the study population and relevant subgroups.
- Define treatment regimens to be included.
- Define outcomes of interest.
- Identify trials that will be pooled in a prospective manner.
- Use only properly randomized trials.

Include all patients randomized in each trial.

Prespecify valid statistical methods to combine data.

Determine the primary endpoint as well as the effect size necessary to be clinically meaningful.

The ISE should have a description of the entire efficacy database's demographics and baseline disease characteristics. Subgroup analyses for age, race, gender, and other characteristics should be looked at by pooling data over different studies of the same dose regimen. The intent-to-treat population should be the focus; however, if there is a large number of discontinued patients or major protocol violators, the results from a "clean" subpopulation, valuable for efficacy, should be presented as well.

The pooled results should always be presented in combination with the individual study results. This allows the examination of the degree of heterogeneity between the studies.^[7]

INTEGRATED SUMMARY OF SAFETY

The summary of safety data is an important and very large part of a new drug application. It is important to investigate the safety data thoroughly through pooling to search for rare adverse events. For example, if an adverse event rate is truly only 1%, then more than 300 patients are needed to observe it with 95% confidence. This is from "the rule of three," which states: If none of *n* patients shows the event of interest, then the upper 95% confidence limit is approximately $3/n$. So if the event were truly rare, say 0.01%, then 30,000 patients would have to be observed, which is larger than most randomized clinical trials. It is also important to estimate accurately the expected rate of any common adverse event associated with the use of the drug.

The International Conference on Harmonization guideline^[2] states that all safety data need to be examined thoroughly to uncover any indications of potential toxicity, and to follow up any indications by searching for an associated supportive pattern of observations. The combination of the safety data from all human exposures to a drug should provide the main source of information, because its larger sample size provides the best chance of detecting the rarer adverse events and, perhaps, of estimating their approximate incidence. However, incidence data are difficult to evaluate without a natural comparator group; so a section on the examination of safety from the controlled studies alone is particularly useful. The results from the controlled studies should be combined separately for placebo and active controlled studies.

The components of an ISS should include the extent of exposure, characteristics of the population, deaths, drop-



out analyses for serious or potentially serious adverse events, rates of common adverse events, as well as clinical laboratory results. All indications of potential toxicity arising from statistical exploration of the data should be reported. The evaluation of the reality of these potential adverse effects should take into account the issue of multiplicity arising from the numerous statistical comparisons made. The evaluations should make use of survival analysis methods to exploit the potential relationship of adverse events incidence to duration of exposure and follow-up. The risk associated with identified adverse events should be appropriately quantified to allow a proper assessment of the risk/benefit relationships.

There are at least three reasons to pool data across studies for the safety summary. One goal is to improve the precision of the incidence estimates. This is especially important for rare events. A second goal is to improve the statistical power for detecting any risk factors that may be associated with the use of the drug and the adverse effect. A final goal is to generate hypotheses about risk that may be explored in future studies.^[8]

It is appropriate to consider carefully the pooling strategy. It is more appropriate to pool studies of a similar design. One needs to consider the patient population, dosing regimens, duration of exposure, and study methods prior to pooling. Furthermore, pooling may not give a meaningful incidence rate if the incidence rates in the individual studies differ dramatically. The differences may be important predictors of the event and should not be ignored. An example of this may be a drug for which phototoxicity was observed. Outpatient studies may reflect the adverse event, while inpatient studies would not. Therefore they should not be combined. If the incidence rates are comparable, then pooling to get a more precise estimate is appropriate.^[8]

Once the pooling has been decided and appropriate patient samples have been obtained for estimating incidence, it is important to consider important predictive factors, such as dose, plasma level, duration of treatment, concomitant medications, age, sex, and concurrent illness, among others.^[8] These factors should be looked at in combination, as well. For example, elderly patients with severe disease may be more prone to a particular side effect, especially when treated simultaneously with a particular concomitant medication. These three-way interactions are difficult to detect and require large sample sizes, and it is exactly the type of information that the clinician is interested in.

CONCLUSION

During the design of a clinical program, careful attention should be paid to the uniform definition and collection of

measurements that will facilitate a subsequent interpretation of the series of trials, particularly if the data are likely to be combined across trials. A common dictionary for recording medication details, medical history, and adverse events should be selected. A common definition of primary and secondary variables is nearly always worthwhile for replication of results. The manner in which key variables are collected, the timing of assessments, the handling of protocol violations, and the definition of prognostic factors should all be kept compatible. To change these items from trial to trial makes it difficult to summarize them into a consistent story. Changes should be made only when there is a compelling reason to do so.^[2]

Integrated summaries are the ultimate conclusion for the benefit/risk ratio of the drug therapy in humans. These are the endproduct for a typically long period during which clinical studies are performed. Therefore it is important to plan the summaries early in the clinical development program. In this way, each clinical study can be planned so that it will fit clearly into the ISE and/or the ISS and will thus be easier to design. If we "begin with the end in mind,"^[9] the plan for the integrated summaries should be written in advance and should evolve as new results are obtained.

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