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Describing the Endpoint: Consistency Across Protocols, Study Reports, Postings, and Publications

Yeshi Mikyas, PhD[1]

Abstract

Endpoints are the cornerstone of clinical trial design and are the critical elements for evaluating the success of a clinical study. Endpoints are communicated in clinical protocols, study reports, study registration and result posting sites, as well as publications. It is, therefore, important that endpoints are presented consistently, correctly, and completely. The FDAAA Final Rule expectations of describing endpoints in specific terms provides a way to keep this consistency across all documents.

Keywords

endpoints, outcome measures, outcome variables, protocols, clinical study reports, journal articles

Introduction

Clinical trials are developed with a specific research question in mind; that is, they have specific objectives. A well-defined, clear objective is practical, includes the purpose and scope of the study, and enables the researcher to establish a relationship between the intervention and the desired outcome.[1,2] A study may have more than one objective, often listed in a hierarchical fashion. As objectives are fundamentally important in the development of a clinical trial, they should be clearly stated in the study protocol.

All objectives are supported by endpoints (outcome measure); that is, each objective should have an endpoint that maps to it. Endpoints are developed by qualified individuals with expertise in the particular disease area.[3] As with the objectives, endpoints are also (for the most part) specified hierarchically, with the primary endpoint describing the desired outcome of greatest therapeutic effect.[3-6] While the study objectives are more broadly encompassing scientific questions to be answered by the trial, endpoints are more specific measurements that address the objectives.

Direct endpoints, that is, those that directly measure how a patient feels, functions, or survives,[7] are clinically meaningful, while surrogate endpoints act in lieu of direct endpoints (where direct endpoints are not possible or feasible to measure). With the advance in science, increased clinical experience, improved technology, and expanded understanding of what is important to patients, meaningful endpoints for various diseases continue to be developed. The Food and Drug Administration (FDA), European Medicinal Agency (EMA), and other professional societies and interest groups continue to put forth endpoint recommendations that are important in various disease states. In addition, in more recent years, networks are being established in an effort to specify and standardize endpoints for major diseases.[8,9] Such standardization should eliminate redundancy and multiplicity, and provide a means to more broadly compare treatments.

In September 2016, the US Department of Health and Human Services issued the ''Final Rule'' for clinical trials registration and results submission that clarifies and expands on the original FDAAA requirements.[10] Among the requirements is a description of the elements that should be included in describing endpoints[10,11] (similar to Zarin et al[12]). Namely, the key attributes of an endpoint are (1) the name of the specific endpoint, (2) description of the metric used to characterize the specific endpoint, (3) time point(s) at which the measurement is assessed, and (4) method of aggregation (required at the time of results posting).[10,11] The description in the Final Rule is consistent with EudraCT's registration and results entry requirments,[13] and FDA's expectation that the definition of an endpoint include ''the nature, timing, and method of assessment.''[3]

The requirement in the Final Rule allows for a more robust description of endpoints, especially when reporting results. As an instance, endpoint recommendations published for different disease states do not normally have the added elements of the

[1] MedImmune, LLC, Gaithersburg, MD, USA

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Corresponding Author:
Yeshi Mikyas, PhD, MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20870, USA.
Email: ymikyas@kapconsult.com

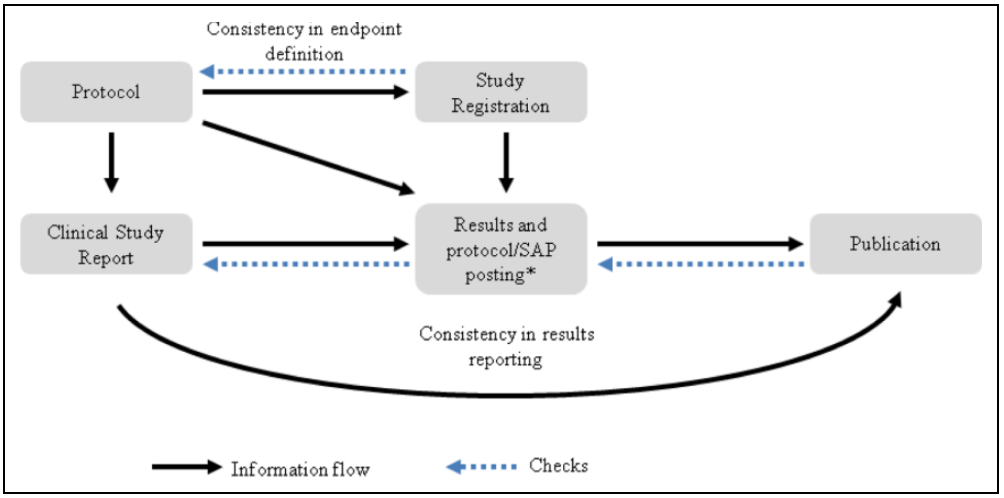

Figure 1. Information flow in communicating endpoints. *Protocol and SAP posting is a requirement of the "Final Rule."

time and *method of aggregation*. For example, in heart failure, *cardiovascular (CV) mortality* is described as a clinically meaningful endpoint in heart failure trials.[14] However, following the Final Rule's expectation, a results entry would be "the proportion of subjects with first occurrence of CV mortality within the 24 months post administration of XX."

The various terms used interchangeably with the "endpoints" may not necessarily add clarity to what an endpoint entails. It is common to see endpoints referred to as "outcome measures" or "outcome variables" or even just "outcomes," so it is tempting to think of them as perhaps just "measures" or "variables," with "outcome" not adding meaningful differentiation. However, as implied by the description above, an endpoint is over and beyond just a measure or variable. While a measure/variable is a numeric value or derived assessment of an event, an endpoint is a variable put into context, within a specific time interval and analytical methods.[15]

Endpoints: Protocol Considerations

The protocol would be the first place where endpoints are spelled out. As trial registration information is extracted from the protocol, it is reasonable to expect that the endpoints stated in the protocol are articulated the same way as what would be posted. Indeed, this consistency is now necessary because the Final Rule requires the submission of the full protocol and statistical analysis plan at the time of results reporting.[10,11] The question is, how often are ClinicalTrials.gov requirements taken into consideration when developing protocols? As it has it, the SPIRIT protocol standard item list[16,17] is one template that recommends describing endpoints consistent with the Clin icalTrials.gov requirements.

Endpoints: Clinical Report Considerations

It stands to reason that if endpoints are articulated in protocols as described above, the results would also be reported in a similar way in the study report. It is a given that there is consistency between the protocol (the design of the study) and the study report (the results of the study). Since the study results are posted on the reporting sites (ClinicalTrials.gov, EudraCT, etc), it is reasonable to expect a one-to-one correspondence between the study report and the reporting sites. There may be instances, of course where certain endpoints may not be detailed in the study report itself (eg, in the case of an abbreviated clinical study report), but the reporting requirements on ClinicalTrials.gov or EudraCT don't differentiate between full or abbreviated reports; results are reported for all applicable studies.

The question is, how often are the protocol registration sites consulted as clinical study reports are developed? Although we often think of study reports as documents prepared primarily for regulatory authorities, the fact that the design and results are posted and shared with the public means it is essential to have consistency across all forums. EMA's Policy 0070[18] and lay language requirements[19,20] are recent examples of additional results/data-sharing endeavors, increasing the demand for consistency in all that is done. As results sharing in different forums become the norm, comparison of content is unavoidable.

Endpoints: Journal Articles

The need for consistency in endpoint presentation across all settings does not end with the posting of results and the fulfillment of regulatory requirements. One or several publications may stem from a single study where the scientific discussion may include some or all of the endpoints. An analysis done by Hartung et al found inconsistencies in the way endpoints were reported between journal articles and results postings.[21] It begs the question as to whether this is because there is a lack of awareness in ensuring consistency in all types of reporting (study report, results posting, journal article), or if there is a lack of awareness of how and what should be reported, or if this is simply an oversight. In an environment where data reporting

and sharing is scrutinized, it is difficult to imagine that deliberately presenting discrepant information would be a decision of choice. In industry, it is quite common to find multiple handoffs with different staff members (often in different departments) working on various aspects of the study and study reporting. Depending on the organization's customary practice, staff may or may not have the awareness of events or requirements downstream (results posting, publications, lay language summaries) or upstream (study registration) in the spectrum of clinical design and data sharing, and what was done and/or what needs to be done. Again, as with protocols and study reports, awareness of the requirements and the need for consistency is also key in the preparation of journal article.

Conclusion

The endpoint description as required by the Final Rule,[10] drives for consistency in articulating endpoints and results across the spectrum of documents prepared in clinical development, including protocols; study reports; study registration; protocol and results postings; and journal articles. This consistency makes it necessary that there is understanding of the downstream requirements and upstream checks in the flow of information (Figure 1). Awareness of these needs and better practices that drive to provide this consistency should help in clinical trial results and data sharing efforts.

Declaration of Conflicting Interests

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