End points in dermatologic clinical trials: A review for clinicians

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Clinical trials are critical for the development of new therapies in dermatology, and their results help determine US Food and Drug Administration (FDA) approval and guide care. Of special relevance is the clinical trial efficacy end point, the metric from which statistically significant outcome is derived. Clinicians' understanding of a clinical trial's end point is necessary for critical analysis of the trial results and for applying those results to daily practice. This review provides practical knowledge and critical evaluation of end points used in treatment approvals by the FDA. The end points for actinic keratosis, acne vulgaris, atopic dermatitis, onychomycosis, and cutaneous ulcer serve as examples. (J Am Acad Dermatol 2016;75:203-9.)

Key words: acne vulgaris; actinic keratosis; atopic dermatitis; clinical trials; cutaneous wounds; end points; onychomycosis; randomized controlled trials; wound healing.

Over the past decade, dermatology has become a burgeoning market for the pharmaceutical industry. Clinicians, patients, and payers depend upon a drug's US Food and Drug Administration (FDA)-approved labeling for information on efficacy and safety. The labeling information is based on the results of clinical trials performed with the objective of obtaining marketing approval from the FDA.[1] Ideally, the end points for such studies should be measurable, standardizable, reproducible, and clinically relevant. In the real world, however, some of the end-point measures are not readily or accurately translatable to the practice setting, whereas others represent some but not all of the outcomes desired for a given patient. A working knowledge of the clinical trial data and the primary end points is important for insightful clinical decision making, including evaluating the suitability of a therapy for a given patient and comparing the efficacy between therapies.

The goal of this review is to provide dermatologists with a foundation for practical understanding of the applications and pitfalls of FDA-mandated end points, particularly for dermatologic diseases that showed high prevalence[2,3] and/or high cost[4]: acne vulgaris, atopic dermatitis (AD), actinic keratosis (AK), fungal infection (ie, onychomycosis), and cutaneous ulcer.

Abbreviations used:

AD:	atopic dermatitis
AK:	actinic keratosis
FDA:	US Food and Drug Administration
IGA:	Investigator Global Assessment

TYPES OF END POINTS USED IN CLINICAL TRIALS

Key points

- **FDA-accepted end points can be divided into 3 broad categories: clinical (direct), surrogate (indirect), and composite.**

The FDA provides guidance for clinical trials intended for seeking drug or device marketing approval. Phase I trials are conducted in small groups of subjects (20-80) with the purpose of collecting safety information.[1] Phase II trials are randomized controlled trials, involving several hundred people with the targeted indication, to evaluate the safety and efficacy of selected doses or dosing schedules of the drug.[1] Phase III trials, known as the "pivotal

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trials," are randomized, multicenter trials of even larger numbers of people with the goal of confirming the safety and efficacy of a single drug dosage for the condition studied.[1] Generally 2 independent, large, phase III trials are required for treatment approval.[1] Although early-phase studies sometimes use study end points different from those recommended by the FDA, almost all pivotal trials use end points recommended by or agreed to by the FDA (Table I). The design of the trial is powered around primary end points; any additional event(s) of interest or secondary end points may be analyzed to help interpret or support the findings of the primary end points. The FDA does not approve drugs based on secondary end points when the primary end points are not met. To be approved, a drug needs to demonstrate superiority in reaching the primary end point(s) over the placebo or control treatment by standard analysis controlling for alpha or type 1 error (ie, in a 2-tailed analysis, a P value of <0.05 is considered significant).

CAPSULE SUMMARY

- The FDA has disease-specific recommendations for pivotal trial end points.
- For some diseases, the FDA has stringent end point requirements with limited real-world applications; for others, the end points are less precise, resulting in high intertrial variability.
- Understanding of the metric of efficacy for clinical trials is important for real-world application of therapies.

The efficacy end points of treatment in a clinical trial may be classified as clinical (direct), surrogate (indirect), and composite. A direct end point (Table II) is an outcome that directly measures symptoms, functional status, or survival of the affected individual.[5] An indirect or surrogate end point (Table I) is a numeric measure such as a laboratory value that is used as a substitute for a direct clinical end point,[5] and is considered able to predict the ultimate desired clinical outcome. Surrogate end points are used with the aim of decreasing the expense and expediting the trial; they are useful in cases of diseases with low event rates, such as using progression-free survival as a surrogate for mortality in melanoma trials.[1] For a surrogate end point to be valid, the changes produced on a surrogate end point are expected to reflect the ultimate changes that will be produced in the direct clinical end point.[5] This is especially demanding as the surrogate may only measure one of several therapeutic mechanisms of action affected by the intervention, and the surrogate in some instances is unlikely to reflect toxicities or allergic reactions. A surrogate end point can be used for drug approval only if it is well validated or to be used for approval of drugs that are "intended to treat serious or life-threatening diseases and that either demonstrate an improvement over available therapy or provide therapy where none exists."[6] In these situations, the FDA may grant approval based on an effect on a surrogate end point that is reasonably likely to predict clinical benefit "based on epidemiologic, therapeutic, pathophysiologic, or other evidence."[6] In dermatology, with the exception of the use of the vasoconstrictor effect for approval of topical corticosteroids, the use of a surrogate end point has been relatively uncommon, having been predominantly accepted for potentially life-threatening, oncologic diseases, such as melanoma[7] and cutaneous T-cell lymphoma.[8-11] In recent years, examples include trametinib/dabrafenib (2014),[12-14] romidepsin (2011), denileukin diftitox (2008), and talimogene laherparepvec (2015).[15]

A composite end point (Table II) is a single measure of effect based on a combination of individual outcomes, which may be clinical or laboratory assessments. The use of composite end points is useful in therapies that have multiple, related benefits, or if individual component events are too infrequent over the course of a trial. For a composite end point to be suitable for a study of a disease, each component event should be clinically meaningful and each component should ideally be equally meaningful.[5] An example of a composite end point in dermatology is demonstrated in its use in the accelerated approval of a systemic therapy for cutaneous T-cell lymphoma, where the trial included a composite end point measurement of skin, lymph node/visceral involvement, and Sézary count.[8,9] One of the pitfalls of composite end point is that statistical significance can be driven by a large effect of a less meaningful component.[16,17] For instance, the treatment may seem efficacious in improving the composite end point if it causes a dramatic improvement in skin involvement, with or without a significant improvement in the other arguably more prognostically relevant, components of the composite end point such as lymph node/visceral involvement or Sézary count.

CLINICAL TRIAL END POINTS FOR COMMON DERMATOLOGIC CONDITIONS

Actinic keratosis

Key points

- **The primary end point for of AK treatments is 100% clearance within the treatment area (typically 25 cm^2).**