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Data considerations in ischemic stroke trials

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Abstract

Data drive the analyses of any ischemic stroke trial, culminating in the main results and potential next steps. The distinct purpose of a given trial, advancing a novel treatment or examining routine clinical practice, determines the nature of essential data elements. Information gathering for an effective trial depends on ample data, adequate infrastructure, and properly planned statistical analyses. This review highlights the fact that successful future trials will require appropriate expertise that extends far beyond these basic considerations in order to move from identification of basic risk factors that are associated with outcomes to knowledge of pathophysiology and causation of outcomes. Efficient and productive data collection by local and central sites must be complemented by expert core lab adjudications. Source data archiving, including complete DICOM imaging datasets or biological specimens, are needed to maximize the potential for study interpretation and financial investment. Standard terminology, such as common data elements and definitions, enhance study comparisons. Screening logs attest to generalizability of a study. Real-time data transmission and core lab evaluation will be critical to guide adaptive trial design. Despite the overwhelming focus on the intervention in a particular treatment trial, individual pathophysiology must be considered. Understanding individual subject characteristics is a tenet of the coming era of precision stroke care, where the course of a given patient and eventual outcome is paramount. This will require a new approach to data collection in clinical trials.

Keywords

Stroke; Clinical trials; Data; Outcomes; Treatment; Precision

Introduction

Data drive the principal and secondary analyses of any acute ischemic stroke trial, culminating in the main results and potential next steps. The distinct purpose of a given trial,

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advancing a novel treatment or examining routine clinical practice, largely determines the nature of essential data elements. Trial design provides the rationale for inclusion of selected variables and dictates that data collection and subsequent analyses are performed with efficient methodology to answer the primary hypothesis.[1]

The plethora of negative stroke trials throughout the last several decades, however, has created a recurring tradition where subgroup analyses are subsequently sought to guide the next generation of trials.[2,3] These subgroup analyses are generally underpowered and all too often, potentially influential data elements such as imaging or other biomarker data are not available as they were not viewed as critical to answer the primary study hypothesis. Each trial, however, does offer the opportunity for valuable data to be collected in systematic fashion regarding myriad aspects of stroke. In this article, we underscore the importance of how such data from successive trials may broaden our understanding of stroke pathophysiology and identify novel therapeutic avenues.

Data

The concept of data has evolved over several decades, in line with discovery of novel risk factors and recognition of particular baseline characteristics that may influence outcomes. The recent era of stroke trials has been focused on identification of prognostic variables that are strongly associated with subsequent clinical outcomes, yet the underlying pathophysiology or rational basis for such a prominent effect remains elusive. For instance, age and stroke severity figure so prominently in prediction algorithms that these two variables have been used as key elements in a novel scoring system to predict outcomes after acute ischemic stroke.[4] Despite repeated analyses of trial datasets that identify age and stroke severity at baseline as influential factors, relatively few to no studies have actually proven a causal relationship or explained why these variables factor so prominently. Furthermore, these selected variables may be useful in generalizing outcome prediction across a large population. However, they may be useless in accurately predicting outcome of an individual stroke patient, which is where our efforts focus on a daily basis. As a result, investigators require novel factors that provide more clarity, expanding our search toimaging or genomic patterns and increasing dimensions of data.

Successful future trials will require unique data and expertise in order to move from identification of basic risk factors that are associated with outcomes to knowledge of pathophysiology and causation of outcomes. Such expertise will also require statistical savvy for a deeper understanding of how such variables relate in clinical context. For example, recognition that baseline stroke severity is a prominent determinant of outcome is rudimentary, yet understanding how particular factors such as collateral circulation determines stroke severity is more closely related to pathophysiology and, hopefully, more likely to lead to new treatment.[5]

Why

The question of why particular variables are influential in stroke outcome is critical. Ongoing stroke trials assume that outcome is directly dependent on the choice of treatment intervention, yet if one fails to understand why certain patients have better or worse

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outcomes, then unraveling pathophysiology is impossible after trial completion. Successive stages of trial design from translational steps to clinical trials must ideally intertwine phases where mechanism of therapeutic interventions can be worked out before larger randomized studies ask the simple question of whether a particular treatment works. Collection of specific data elements may help unravel pathophysiology as well as bolster claims of a promising therapeutic mechanism, rather than a simple comparison of randomized study arms.

What

The menu or potential scope of data elements to be collected in trial design has multiplied in recent years, from a basic set of clinical variables to addition of imaging, physiologic, and genomic data.[6] Even when specific markers or detailed datasets are of unproven value, collection of source data has proven invaluable. For instance, stroke imaging studies have failed to discern the most critical exact volumes of infarct core or ischemic thresholds. Collection of source imaging datasets would allow for repeated analyses and has proven invaluable.[7–16] Similarly, collection of biological samples such as blood constituents does not require knowledge of every molecular signature, as storage of samples may be tapped decades later to identify novel findings. Source data archiving, therefore, ensures maximal study interpretation and financial investment. Digital Imaging and Communications in Medicine (DICOM) imaging datasets and biological specimens may be tapped for years to come. Clinical variables, however, require meticulous definition to preserve future value. For instance, the presence of diabetes may be qualified on various definitions, from historical aspects to physiologic measures such as measurement of a hemoglobin A1C level. The development of common data elements for inclusion in a given study therefore provides a standard language to define what each variable reflects.[17]

Where

Application of standard definitions such as the common data elements is not enough to insure rigorous data collection and interpretation. The location or environment where data are collected is also an essential consideration.[17] Local collection of data elements in real time is quite different from central adjudication of identical variables. Imaging interpretation provides the most common example of such distinction based on environment of data collection. Determination of the extent of early ischemic changes on CT or the degree of reperfusion may vary considerably between local and central readings.[18] It should be emphasized, however, that both local and central readings serve important roles. Local readings conducted in real time by treating physicians enhance the generalizability of subsequent data analyses. Alternatively, central adjudication of imaging features by expert core lab investigators provides reliability.

Who

The source of data collection is equally important, as an expert investigator does not provide the same data quality as a novice. Standardization may be achieved through certification in scale application or rating systems. Certification of rating systems in stroke trials now include application of the National Institutes of Health Stroke Score (NIHSS), the Alberta

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Stroke Program Early Computed Tomography Score (ASPECTS), and the modified Rankin scale.

The question of 'who' also applies to the subject population, as selection biases have considerably warped our perspective on stroke. For instance, knowledge of the denominator population via screening logs is a critical element of trial design. Understanding the nature of who was excluded from a trial is just as important as analyzing the final trial dataset. Screening logs are critical for ultimate interpretation of any stroke trial and allow interpretation of the scope of generalizability. Similarly, once selected patients are included in a trial, consideration of dropouts or withdrawal of care is key.

When

The timing of data collection is also relevant. For example, specific variables may have different meaning depending on whether they were measured in the acute period of stroke onset or in the follow up of anacute stroke case, and the timing must be precisely identified. For instance, clinical trials often refer to 'admission' values for blood pressure or NIHSS severity, yet it is not entirely clear when this time point takes place. Such measurements are known to change considerably over time and even the detection of fluctuation in these parameters may be an important feature of a given stroke patient. There is also excessive focus placed solely around the time of the acute stroke 'intervention'. Collection of data centers heavily around the timing of the investigational treatment and there are often very few surveillance data on other phases of care such as the prehospital, intensive care unit (ICU), or post-discharge periods up until the standard day 90 evaluation. As a result, there has been negligible focus to date on potentially critical treatment variables such as the early hemodynamic management, ICU treatment, or rehabilitation therapies that may influence clinical outcomes in stroke. The timing of data collection, transmission and adjudication should closely parallel the corresponding events in the course of a given trial subject. Trial design should allow for unexpected protocol changes to be implemented as they evolve as a result of continuous collection and analysis of data. Maximal knowledge may be gained from a stroke trial when interval events are considered in a timely fashion rather than adhering to a rigid protocol for years until the final analyses may be conducted.

Contemporary Data Considerations

The recent publication of many acute stroke trials and the bevy of corresponding critiques that shortly followed underscore the critical nature of data considerations in trial design.[19,20] Most recent critiques highlight shortcomings in data provided or accounted for in these studies. Endovascular trials have been criticized for incomplete documentation of vascular occlusion site and other angiographic features. Similarly, the timeline of procedural steps has often been incomplete or inconsistent across trials. In the future, use of the NINDS Common Data Elements should minimize such disparities and allow for greater value of the resulting dataset.[17] Discrepancies in data across trials limit comparisons and undercut the interpretation of meta-analyses subsequently conducted.

A balanced combination of appropriate infrastructure, extensive data collection, and clinical expertise are therefore essential in any stroke trial, even before statistical aspects of data

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analyses are considered. Modern stroke trials must be able to collect clinical, imaging, and other biomarker data in appropriate clinical context. The history of stroke trials has unfortunately culminated in an abundance of negative primary results. Large datasets will be increasingly important in coming years as the concept of precision medicine is implemented in stroke care. Understanding individual subject characteristics is a tenet of the coming era of precision stroke care, where the course of a given patient and potential pivotal determinants of their eventual outcome are paramount. This review highlights new approaches to help realize these results.

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