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Issues in regulatory guidelines for data monitoring committees

David DeMets^a, Robert Califf^b, Dennis Dixon^c, Susan Ellenberg^d, Thomas Fleming^e, Peter Held^f, Desmond Julian^g, Richard Kaplan^h, Robert Levineⁱ, James Neaton^j, Milton Packer^k, Stuart Pocock^l, Frank Rockhold^m, Belinda Setoⁿ, Jay Siegel^o, Steve Snapinn^p, David Stump^q, Robert Temple^r and Richard Whitley^s

As clinical trials have emerged as the major research method for evaluating new interventions, the process for monitoring intervention safety and benefit has also evolved. The Data Monitoring Committee (DMC) has become the standard approach to implement this responsibility for many Phase III trials. Recent draft guidelines on the operation of DMCs by the Food and Drug Administration (FDA) have raised issues that need further clarification or discussion, especially for industry sponsored trials. These include, the time when DMCs are needed, the role of the independent statistician to support the DMC, and sponsor participation at DMC meetings. This paper provides an overview of these issues, based on the discussions at the January, 2003 workshop sponsored by Duke Clinical Research Institute. *Clinical Trials* 2004; 1: 162–169. www.SCTjournal.com

Introduction

The randomized clinical trial has become the central research tool for evaluating new drugs, biologics, devices and procedures for regulatory review and approval. Many issues in the design, conduct and analysis of a clinical trial must be carefully implemented in order to produce a definitive result. A significant component of this process is the ongoing interim review of the progress of a trial including recruitment, adherence to treatment, participant safety, intervention benefit and overall trial quality. Following the unfortunate death of a patient in a gene transfer trial, which raised considerable concern in academia, government and industry as well as among the general public, the Secretary of Health and Human Services wrote that all trials should have a monitoring plan. Further, those trials that recruited high risk patients, used new

innovative interventions or had serious irreversible outcomes may require special surveillance [1]. By 1998, the National Institutes of Health (NIH) had already established a policy that all of the trials they fund must have a monitoring plan [2] and that all Phase III trials must have a committee of experts, separate from the trial investigators and leadership, often called a Data Monitoring Committee or DMC. Many names for such a body have been used such as Data and Safety Monitoring Boards or Safety and Efficacy Monitoring Committees, but the function is typically the same. The NIH provides guidelines for their funded trials with respect to the creation and operation of a DMC [2]. In November of 2001, the FDA issued a draft guidance document on the formation and operation of a DMC for sponsors of trials subject to FDA oversight [3]. In most areas, the guidance is consistent with procedures followed by NIH-funded trials. While a guidance document is not

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a mandate (i.e., it is not regulation), it does provide a standard for industry sponsored trials to consider and is likely to influence how such trials are monitored and reviewed.

The goal of a DMC is to monitor many important aspects of the trial such as progress in patient recruitment, protocol compliance and data quality, but it needs to pay special attention to patient safety [4]. In addition, for some trials important primary outcomes such as death, myocardial infarction, stroke or cancer recurrence may reflect both benefit and risk. When early evidence for benefit or risk becomes convincing, the DMC may recommend trial termination. Such a process not only protects human subjects from unnecessary exposure to harmful treatments, but also leads more quickly to public access to beneficial treatments. An independent external DMC can preserve the validity and credibility of a trial not only for regulatory approval but also for acceptance in the medical community. DMCs do not typically assume responsibility for site monitoring although they may well review the results of such audits.

This paper is based on a workshop sponsored by Duke Clinical Research Institute (January 17–18, 2003) to discuss several controversial issues that have arisen recently, primarily in response to the FDA draft guidance document.

NIH tradition

The Greenberg Report, commissioned by the National Heart Institute in 1967, developed the framework for the organization and structure of multicenter clinical trials [5]. The report made several recommendations, including some relevant to the monitoring of clinical trials. Among these was the recommendation that a trial should have an advisory committee of scientific experts in the field who explicitly do not contribute patients to the trial. The report also recommended that a mechanism be developed for early termination based on emerging evidence of harm. Furthermore, early termination "might be contemplated if the accumulated data answer the original question sooner than anticipated, if it is apparent that the study will not or cannot achieve its stated aims, or if the scientific advances since initiation render continuation superfluous". The report also said that the NIH should not initiate such action without the advice and recommendation of external consultants.

The Coronary Drug Project (CDP) was initiated in 1962 to investigate the effect of several lipid lowering drugs on cardiovascular mortality and morbidity [6]. At the outset, the CDP established a Policy Advisory Board that was to advise on policy questions relating to design, drug selection,

ancillary studies and investigator selection. In 1968, this Board recommended that a Safety Monitoring Committee periodically review confidential data. This committee had representatives from the statistical data coordinating center, the National Heart Institute at NIH and academic experts in biostatistics, clinical chemistry, and cardiology. This Safety Monitoring Committee reviewed accumulating data in depth at regular intervals and reported to the Policy Advisory Board who in turn made recommendations to the Institute and ultimately to the investigators. The CDP experience [7] provided important lessons about the process of monitoring accumulating data.

Since the time of the CDP, with a few exceptions, the National Heart, Lung, and Blood Institute has combined the functions of the Safety Monitoring Committee and Policy Review Board into a single external committee for the monitoring process, referred to as a data and safety monitoring board (DSMB) or, more simply, a data monitoring committee (DMC).

During the three decades since the CDP, the Greenberg model has been adopted by other institutes at the NIH, but with many variations [8]. The National Eye Institute was among the first, but others soon followed. Through their AIDS Clinical Trials Group the National Institutes of Allergy and Infectious Diseases (NIAID) contributed the concept of the open, closed and executive committee sessions of the DMC and also pioneered the use of a single DMC reviewing multiple trials [9]. By the early 1990s [10] the typical DMC for NIH sponsored trials included clinicians with medical and clinical trials expertise, biostatisticians, and ethicists; some trials included members from other disciplines, such as epidemiologists and pharmacologists. Notably, the role of institute staff varied considerably among institutes. Another survey conducted in 1995 found that of 42 single center NIH sponsored trials, about one-third had a DMC while three-fourths of the 82 multicenter trials had a DMC. In 70% of the cases NIH appointed the DMC members. NIH program staff involved with the trial usually attended the entire DMC meeting. Industry and FDA representatives attended open sessions occasionally. The trial leadership attended the entire DMC meeting 30% of the time and the open session about 55% of the time.

FDA guidance

The FDA provided draft detailed guidance on the role and conduct of clinical trial DMCs in November 2001 [3]. FDA regulations contain only one mention of DMCs; such committees are required for certain emergency research studies in which informed

consent is waived, as part of an extra set of protections that are believed necessary in this situation [11]. In FDA guidance prior to the November 2001 issuance, DMCs were mentioned only briefly. In the 1988 document entitled "Guideline for the format and content of the clinical and statistical sections of an application" [12] the FDA briefly mentions the data monitoring process and the existence of DMCs, but provides little detail as to structure and function. The International Conference on Harmonization (ICH) guidance documents, particularly E6 on good clinical practice [13] and E9 on statistical principles for clinical trials [14] provided a bit more detail, especially with respect to statistical monitoring issues.

The 2001 draft guidance is by far the most detailed and definitive statement by the FDA on this issue. The guidance was motivated, in part, by the Office of the Inspector General (OIG), US Department of Health and Human Services, which issued a report in 1998 on Institutional Review Boards (IRBs) that included a recommendation that DMCs be required for trials under NIH and FDA purview, with details left up to the NIH and FDA [15]. The OIG report followed the widely publicized death of a patient participating in a gene therapy trial, noted earlier. A FDA working group with representatives from the three Centers for human medical products – drugs, biologics and devices – was formed to develop a guidance document on DMCs. Input was sought from external experts on an interim draft of the document; comments were also solicited from NIH later in the process. The draft document was open for public comment for three months following its publication in the Federal Register. These comments, together with discussion at an open public meeting held shortly after the document was issued, will be used to revise the current 2001 version.

The intent of the FDA DMC guideline is to set forth, in general terms, acceptable models for DMC establishment and operation, to describe advantages and disadvantages of different approaches, and to bring attention to special areas of concern. Most of the content of the draft guideline has proven to be noncontroversial. These areas include the different roles of IRBs and DMCs, the multidisciplinary nature of DMCs, the necessity of a DMC charter defining operational procedures, the importance of minimizing DMC members' conflicts of interest and the need for interim data to be kept highly confidential. Three areas, however, have generated substantial discussion: 1) when are DMCs necessary; 2) should the statistician performing the unblinded interim analyses be independent of the study sponsor and/or leadership group; and 3) should the sponsor (especially government) have access to interim data and participate fully in DMC

meetings? Each of these areas will be discussed in more detail.

What trials need an external DMC

One of the concerns expressed by those commenting on the FDA DMC guidance document was that the creation of a DMC will become the default approach, thereby leading to far more DMCs than are needed and potentially exhausting the pool of experienced investigators at the expense of trials for which DMCs are most critical. The guidance makes clear, however, that DMCs are not routinely needed. The NIH generally requires an external DMC for all Phase III trials regardless of risk [2], but NIH-sponsored trials are primarily the type of trial for which the FDA does recommend a DMC, as described below.

The FDA draft guidance document recommends that an external DMC be established for long term trials with mortality or major morbidity outcomes, for trials in which serious adverse events are expected, and for trials with novel and/or potentially high-risk treatments [3]. Early phase trials do not usually warrant an external DMC but may in limited circumstances, such as when they involve a high risk intervention or vulnerable populations [16]. For example, early phase gene therapy trials may benefit from external DMCs because of strong concerns about safety. DMCs are also recommended even for trials focused on a short term outcome such as symptoms if the population under study is at elevated risk for serious morbidity or mortality. For example, a trial evaluating a pain-relieving agent for use in cancer patients would need interim monitoring of comparative mortality data to ensure that the treatment was not hastening death. Such interim monitoring should be done by a DMC. External DMCs are probably not needed for early phase trials that have no unusual safety concerns.

The FDA guidance clearly points out that many drug, biologic or Phase III device trials do need an external DMC. Although not required, many other development programs may benefit from having an internal DMC, perhaps with external advisors, to monitor the overall results across the portfolio of trials, including early phase trials. A committee might consist of employees of the sponsor working on different projects, and thus affording some independence or distance from the project and its developers. These committees would not look at unblinded data for pivotal trials, but could consider accumulating data suggesting additional trials or looking for dose-related problems and can operate with less formality so long as the trials under their review are not major randomized, controlled trials

expected to serve as the primary basis for marketing approval.

The relationship between independent DMCs and local IRBs is not well established. Although the FDA guidance document does explain that only DMCs should be examining interim comparative data, the lack of clear delineation of responsibilities for human subjects' protection often leads to confusion and different perspectives among sponsors, DMC members and the local IRBs [17–20].

The independent statistician

In order for a DMC to meet its responsibility to ensure the ongoing safety of patients participating in a trial, as well as of future patients who may enter the trial, it must have available interim analyses that evaluate relevant data from the ongoing trial, usually in an unblinded fashion. A statistician needs to be assigned the task of producing such interim analyses. The FDA guidelines suggest that it is optimal for this responsibility to be assigned to a statistician independent of the sponsor as well as any other entity with decision-making authority, such as a Steering Committee. The FDA guidelines agree that any other arrangement has a greater risk of unblinding the decision making party which could lead to bias in future decisions concerning the conduct of the trial. The concept of the independent statistician as put forward in the FDA document is relatively new and does not reflect the common practice in NIH sponsored trials or many industry sponsored trials; thus it has generated some discussion and concerns [21–28].

In order to understand the issues surrounding the "independent statistician" concept, it is important to recognize that there are typically at least three different roles for statisticians in a multicenter Phase III trial sponsored by a pharmaceutical company but led by a Steering Committee consisting of academic leaders and sponsor representatives [2]. Statisticians: 1) collaborate on the design of the trial and perform the final analyses as part of the trial Steering Committee; 2) serve as a nonvoting member of the DMC to perform the interim analyses to be considered by the DMC; and 3) serve as a voting member of the DMC in order to review trial conduct and interim results, and advise the DMC regarding the statistical interpretation of these results. The sponsor statistician often is responsible for the general statistical design in the early drafts of the protocol. Once the investigators are assembled, a Steering or Executive Committee is formed which may also include an academic based statistician, although in some cases the sponsor statistician may also serve in that role. Often the Steering Committee statistician(s) develop the statistical analysis plan

and are jointly involved in the analysis, interpretation, and publication of the final results.

The DMC statistician is an individual who does not work for the sponsor, has no vested interest (financial or otherwise) in the outcome of the trial and is not participating in the trial in any way other than that of DMC member. This individual is usually experienced in clinical trial design and analysis, and in particular with the statistical methods for monitoring accumulating interim data. A major responsibility of this statistician is to help and advise the rest of the DMC on the interpretation of the interim analyses, but the responsibilities of this statistician typically do not include performing the interim analyses.

The independent statistician, as defined in the FDA guidance document, is the individual responsible for the analysis of the interim results and for presenting that analysis to the DMC. According to the FDA guidance document, the independent statistician should neither work for the sponsor nor have any major role in the operational conduct of the trial. This individual is bound to the same confidentiality as the members of the DMC with regard to the interim data.

The rationale for requiring the independence of the statistician performing the interim analysis [2–4] and therefore having access to unblinded data, is the preservation of trial integrity and credibility. The statisticians advising the Steering Committee and the sponsor on trial progress, possible design changes or changes in the final analysis plan should not be aware of emerging interim results. Knowledge of interim results may influence decisions on any proposed changes in the primary outcome variable, duration of trial recruitment and follow-up, or the analysis plan and thereby introduce bias. Inclusion of an independent statistician provides some insurance against such actual or perceived bias. The benefits of protection from bias that an independent statistician affords can be quickly lost if the statistician is not familiar with the protocol, the clinical database, the disease, and the outcomes under study. If this is not the case, the possibility of errors in the analysis, or misunderstandings between the DMC and the statistician on whom they rely for interim data analysis, may be increased.

While the separation of the independent statistician and the Steering Committee and sponsor statistician has become more common in industry sponsored trials, it is relatively rare in NIH sponsored trials. There are many variations on the implementation of the different statistical roles in NIH and industry sponsored trials. As the NIH clinical trial model evolved from what was originally described in the Greenberg Report [5], a structure developed that has been typical in many

NIH sponsored clinical trials (Figure 1). In this structure, most of the statistical activity takes place within the data coordinating center. The senior statistician at the coordinating center often shares the responsibility, or may even be primarily responsible, for the trial design by serving on the Steering Committee. In addition, this statistician is also responsible for conducting the interim analyses and presenting those analyses to the DMC. Thus, one individual interacts with both the Steering Committee, which is blinded to the interim results, and with the DMC, which reviews the unblinded analyses.

There are some advantages to the approach of having one statistician at the coordinating center play two roles: Steering Committee statistician and interim analysis statistician. The primary statistical responsibility is in the hands of the statistician with the most knowledge of the protocol design, the data collection process and the accumulating results. Thus, the reports to the DMC will be developed and presented by the statistician who is most familiar with all aspects of the trial. Most importantly, those who support the NIH traditional clinical trial model argue that the potential risks for introducing bias are outweighed by the benefits of having the statistician most knowledgeable about all aspects of the trial – the protocol, the Steering Committee's point of view, the treatments under study and the types of data being collected – perform and present the interim analyses to the DMC.

While there is a long and successful history of NIH trials using this approach, concerns about introducing bias in Steering Committee decisions during the conduct of the trial have begun to emerge, especially in industry sponsored trials. In fact, long before the FDA issued its guidance document, as industry sponsored multicenter Phase III trials with serious clinical endpoints became more common, a modified approach to the traditional NIH model was adopted by many investigators experienced in conducting NIH sponsored trials [29]. This modified clinical trial

Figure 1 National Heart, Lung and Blood Institute clinical trial model

model for industry is depicted in Figure 2. The principal difference between the two models is that the trial coordinating center has been logistically divided into two units, one being a trial data management coordinating center and the other a statistical analysis center. In this industry sponsored trial model the data management and coordinating center is responsible for collecting, editing and managing the various databases while staff remain blinded to outcome data by intervention assignment. This activity may be performed by staff of the industry sponsor or by an external contract research organization (CRO) specializing in trial management. A statistician connected with this activity could be involved in trial design and serve on the Steering Committee. The statistical analysis center would be a separate unit from the data management coordinating center that may reside within the industry sponsor, at an external CRO or at an external academic center. The statistician at that center does not serve as the Steering Committee statistician. The statistical analysis center obtains data from the data management coordinating center periodically (e.g., monthly) and performs safety reports and DMC interim analyses reports as required. The independent statistical center statistician interacts with the data management center as needed to resolve data queries resulting from analyses and to remain current as to general data flow. The Steering Committee and sponsor statistician may be involved with the data management and coordination center but not the statistical analysis center. The separation essentially establishes the statistician at the statistical analysis center as the independent statistician. Numerous industry-sponsored clinical trials in several disease areas have now used this model successfully [30–32].

Figure 2 Modified clinical trial model

One issue with this modified NIH clinical trial model is whether it is acceptable for the statistical analysis center to reside within the sponsor's domain or whether it should be an external group funded by the sponsor, as recommended by the FDA guidance document. There have been several trials in which a statistician working for the sponsoring company has been the one to perform the interim analysis and present to the DMC [33, 34]. In such cases, this statistician typically has been involved in the design phase along with the primary sponsor statistician, who may also be the Steering Committee statistician. Once the trial is underway, however, an internal administrative separation, or 'firewall', within the sponsor's domain is created between the trial statistician for the Steering Committee and the statistician and other sponsor personnel who will be performing the interim analyses for the DMC. The firewall serves to preserve the blinding of interim results from both Steering Committee and sponsor management. The concern is whether this firewall is truly impenetrable. An advantage of this model put forward is that it protects and facilitates the quality of the data analysis because the statistician performing the analysis is very familiar with the company's data management systems and is unlikely to make errors in using the database provided by the data management group. However, the independent statistician's activity, which may suggest or signal trial issues, can still be observed. For example, frequent meetings or intense analysis outside the expected schedule may indicate to office colleagues that something is going on in the assigned trial.

There is general agreement that it is absolutely essential for the statistician with responsibility for performing the interim analysis and participating in discussions with the DMC to be familiar with the protocol, the types of data being analyzed, and the quality assurance systems in place to provide timely and complete data. Independence cannot mean ignorance. Lack of familiarity could jeopardize the safety of the trial participants, the DMC process, and ultimately the trial itself. As noted, one way to ensure such familiarity would be to include the independent statistician in the study design and the development of data collection plans and quality assurance systems. The independent statistician may also confer, as needed, with the DMC statistician to address statistical issues identified during the interim analyses. The external statistical analysis center concept, involving the 'independent statistician' in the protocol development, has now been widely used and appears to be quite successful [29].

For NIH sponsored trials, the practicality of implementing the independent statistician concept has been a concern to some. The traditional trial coordinating center would have to designate two

trial statisticians: one who was the primary statistical voice on the Steering Committee, and another who will conduct the interim analyses and present them to the DMC. This change should not prove too onerous to implement, however, since most coordinating centers already have some internal structure between those who manage the data and those who must analyze the data. The separation of the independent statistician from those involved in ongoing trial management would require a similar process.

In cases when the independent statistician is internal to either the industry sponsor or the NIH coordinating center, the credibility of the trial will depend on the credibility of the firewall created to ensure that information about interim analyses does not leak to those involved in managing the trial. Little has been written about what constitutes an adequate firewall. This area certainly requires further discussion. To achieve maximum independence, the model of organizationally separating the independent statistician from the Steering Committee and sponsor statistical roles is preferred by the FDA. The choice to consciously apply or not apply this model is an important consideration in the design and organization of a clinical trial.

Sponsor DMC participation

The FDA DMC draft guidance comments on the role that sponsors of trials, either industry or federal, should have in the DMC meetings. The guidance advises that anyone involved in trial management and interim decision making (e.g., protocol changes) should not have knowledge of interim data. For industry sponsored trials, it is reasonably common (but not universal) for industry staff to remain blinded to interim data; NIH staff involved in managing a trial, on the other hand, are usually (but not always) present during both open and closed sessions of the DMC meeting. Thus, if the FDA guidance were followed in NIH sponsored trials, the NIH would have to change its practice in regard to its staff participation in DMC meetings, a suggestion that not unexpectedly has provoked substantial controversy within NIH.

The National Institute of Allergy and Infectious Diseases (NIAID) pioneered and published a format for open, closed and executive sessions followed by a debriefing session [9]. During open sessions, trial progress is discussed with investigators and industry sponsors if involved. Closed sessions involve reviewing not only trial progress but also treatment comparisons of safety and efficacy. For nearly all trials, the principle has been that investigators participating in the trial should not participate in the closed DMC session in order to avoid biases in

patient recruitment, treatment and evaluation, and thereby protect the trial integrity. For the HIV therapeutic trials, NIH staff, who have no responsibilities for entering, treating or evaluating patients, are present during the closed sessions. These staff do participate in protocol team meetings and teleconferences. Their participation in discussions of protocol modification, however, could introduce bias. The DMC may also hold executive sessions for which the statistical center statisticians are excused. Executive sessions permit the DMC to formulate recommendations; in the NIAID therapeutic trials model, limited NIH staff are typically present to observe the deliberations. Considerable variation exists across NIH about what staff may attend executive sessions.

Most NIH trials are not influenced by financial and commercial implications, but there may be other conflicts in these trials. Staff of the NIH do not have the same potential financial conflicts of interest that industry employees might have. However, the Institutes of the NIH and individuals working at the NIH are under budgetary and public pressure to accomplish successful trials that will have important scientific and clinical impact. In addition, the importance of intellectual conflicts should not be underestimated. For example, an NIH scientist serving as a program officer may have a strong belief in the principle being tested in the trial and may be highly invested in a particular outcome.

Recently, the National Heart, Lung, and Blood Institute (NHLBI) has instituted a policy that the Institute must have a representative at the executive sessions but that individual must not be involved in the trial conduct or with any programmatic responsibility for the trial. Such a policy would reduce concerns that involved NIH staff may influence DMC deliberations or recommendations or that any protocol changes introduced by the Steering Committee could be influenced by knowledge of interim results. In some National Cancer Institute (NCI) trials, no staff are present during the executive session while for other trials staff are present. Thus, there appears to be no consistent NIH policy on this issue. Without doubt a more uniform position of the NIH regarding staff participation in the DMC closed sessions would be useful.

While trials have many constituencies including participants, investigators and the general public, sponsors have a financial investment, usually substantial, that is at risk, and they understandably wish to protect their investment. The argument for industry-sponsor participation in DMC closed sessions is that the sponsor has unsurpassed knowledge and understanding of the investigational treatment that should be brought to bear in the protection of patients via the interim monitoring process. For example, the sponsor has more

information regarding the total experience of the drug or device under study than most members of the DMC. Thus, the argument is that sponsor presence can add information to the DMC deliberation and contribute to a better informed set of recommendations. Sponsors often think that DMC recommendations should not be made without some regard to regulatory expectation since the sponsor may be able to add useful information. In addition, arguably, sponsor knowledge of the intervention and the portfolio of other relevant studies can be especially helpful when interpreting and evaluating the accumulating data. Since most of these early phase trials are monitored internally, this knowledge is generally brought to bear on interim monitoring.

The FDA guidelines are specific in their recommendations that sponsors of Phase III trials should not participate in, or even attend the closed sessions or executive sessions of the DMC [3]. The guidance does not differentiate between industry and federal sponsors in this regard. Many investigators having experience with both types of sponsors suggest that the conflicting pressures may be different, but are often still present. The concern that results of interim data may be used in ways that could introduce bias into the trial is relevant for both private and public sector sponsors. For example, considerations regarding changes in the design, such as increasing or decreasing the sample size or changing the primary outcome variables, could be influenced by the emerging results and potentially bias the trial or inflate the Type I error. In addition, early results can be highly variable and thus misleading. Design changes based on interim results, for reasons other than enhancing safety of trial participants, are not recommended in any case.

Summary remarks

Over the past three decades, a great deal has been learned about the role and operation of DMCs. As industry-sponsored trials make greater use of DMCs, some adjustments to the historical modes of operation are needed. These adjustments appear to be quite feasible. The issues discussed here – when and how to use a DMC, the role of the independent statistician, sponsor participation in DMC meetings and DMC member conflicts of interest – all raise interesting challenges that need attention. As with the initial evolution of the DMC, additional experience will likely lead to further useful modifications that will improve the effectiveness and efficiency of DMC operations. It must also be remembered that the primary goal of the DMC is to maximize participant safety. While keeping in mind the guidelines and policies discussed in this

paper, study investigators and sponsors must consider whatever individual trial circumstances are necessary to achieve that goal.

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