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Case Report Form Insanity

By Paul Latimer

The typical case report form (CRF) and, in particular, electronic CRF (eCRF) used in clinical research is seductive in the way it reduces messy clinical realities to nice round integers and categorical answers. In CRF-world, diagnoses, dates and times are definite, even if the real world is not. Unfortunately, most medical conditions are not easily described by checkboxes. It is certainly understandable that biostatisticians want simple answers, but it should not be at the cost of asking simpleminded questions. Leaving a data field empty or indicating uncertainty with a question mark when there is no correct answer is sure to generate a data query. Seldom do eCRFs even offer the option. The resulting data is neat and tidy, but perhaps false and misleading. What is the point of collecting data that does not correspond to reality or is meaningless? If insanity consists of an inability to grasp reality, many CRFs meet the diagnosis.

A few recent examples from our own experience illustrate the problem:

Example 1. In a study of generalized anxiety disorder (GAD), the sponsor had the mistaken idea that the condition is an episodic disorder. In fact, GAD is often a lifetime, chronic condition, waxing and waning over time but never leaving completely. Nevertheless, the study's eCRF insisted on knowing the duration of the current episode. The eCRF ignored our protestations that there was no specific duration for some subjects because there was no specific episode. As a second resort, we input the subject's age. The eCRF rejected this answer out of hand. As a last resort, we entered an arbitrary answer based on the subject's subjective perceptions and fuzzy memories of the most recent waxing. The eCRF thus compelled us to enter a misleading number with no clinical significance, turning a chronic, lifelong disorder into a condition with a discreet, recognizable episode of known duration.

Example 2. The CRF for a bipolar mania study required the exact dates for the beginning and end of every mood episode experienced over the lifetime of the subject. If you have ever treated manic individuals, you know that this level of detail is unavailable, even in medical charts, unless the current mood episode is the first or second the patient has experienced. Because of the cognitive dysfunction associated with bipolar disorder, many patients have frequent mood fluctuations and poor recollection of specific episodes. In any case, what value did these dates have in a drug study comparing two therapies over a discreet time period? Would the approximate number and average duration of previous episodes have been sufficient?

Example 3. The eCRF for a depression study asked about family history of psychiatric disorders. In one case, based on the subject's impressions, I recorded that the mother and a grandmother may have had generalized anxiety disorder. With an almost audible "ah ha!" the eCRF then asked for the date of onset for both individuals. How many people do you know who could provide that kind of detail about their mother and grandmother? Nevertheless, the eCRF required an answer and common sense was no excuse.

Example 4. The CRF for a fibromyalgia study required the date and, believe it or not, the time of adverse event resolutions. How often is the subject supposed to check his/her temperature? What is the clinical rule for determining the exact time when a rash resolves? What is the point of forcing the investigator to make up an answer that is almost certainly incorrect?

As illustrated in the examples above, CRFs often require data that have no relevance to subject safety and could not possibly be useful in an NDA or publication. It is costly and time-consuming for the study team and an imposition on the subjects to collect useless data just because it is easier to throw in useless questions rather than think through how the data will be used.

Rather than fly experienced investigators across the country to listen to a regurgitation of the protocol and 45 minutes of GCP pablum, why not use some of the time for a productive discussion of the CRF and other practical aspects of protocol execution? By putting our heads together, perhaps we can meet the biostatisticians' needs with data that actually means something.

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