

I Don't Look Good in Orange or Stripes

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ABSTRACT

Clinical programmers are often asked by data managers, statisticians, project directors, or their supervisors to hard code or change clinical trials data to match the Case Report Form or other data collection medium rather than to open the database and make the appropriate change(s). However, there are federal regulatory regulations that set forth policy and enforcement of such.

INTRODUCTION

When you, as clinical programmers, are asked to make data changes by others, you are often intimidated by their presence, status, or tone of voice, so you often comply without realizing what they are actually asking of you.

DEFINITIONS

What is hard coding? Hard coding is the programmatic changing of data in a database, without an audit trail, that had been incorrectly data entered from a Case Report Form or other data collection medium.

An audit trail is documentation detailing who made the changes to the database, and when, and why they were made. In 21 CFR 11, the official definition is "a secure, computer generated, time-stamped electronic record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record."

EXAMPLES

I have collected examples of hard coding over the years in hopes that I would one day present this paper. I have retyped the SAS® code and made slight modifications to shield the identity of the programs, drugs, and programmers.

1.

```
***update does all the AE updating/correcting and also all of the corrections for the
other database members. the programs formerly known as aaaa, bbbb, and cccc are all
incorporated in this program. XXX 19xx-xx-xx *** ;
***fixit must run before aeupdt1 as it may affect failure and rx stop dates *** ;
%doseadm(drug=aaa) ; * adds new dosing info;
%doseadm(drug=bbb) ; * adds new dosing info;
%fixit ; * makes database corrections;
%aeupdt1 ; *do AEs stop treatment;
%aeupdt2 ; *adds new AEs and MedDRA grades, creates AE database. Does fixes + ;
%stdtfix(drug=aaa) ; *fix sched start date for drug aaa;
%stdtfix(drug=bbb) ; *fix sched start date for drug bbb;
```
2.

```
"if SUBJID='1525' & AESTDTC='2005-01-06' then AESTDTC='2006-01-06';"
"if SUBJID='1525' & AEENDTC='2005-01-15' then AEENDTC='2006-01-15';"
```
3.

```
"if SUBJID='511' & AEENDTC='2003-09-23' & AEPTCD in ('0053','0088') & AETOXGR='5' then
AETOXGR='3';"
```
4.

```
"if SUBJID='524' & AEENDTC='2005-12-23' & AETOXGR='5' & AEPTCD='0643' then delete;"
```
5.

```
"if EXDOSE > 98 then EXDOSE =.;"
```

And the list goes on and on.

How dangerous are all of these real-life examples? In Example 1, someone just looking at the program with the comments might think that the program should have the database opened and corrected. In Example 2, the start and end date of an Adverse Event is changed by a full year. In Example 3, the toxicity grade (severity) is changed for two adverse events – from fatal to severe. One can only hope there is not a death record elsewhere in the database! I shudder to think about Example 4. And, I would think that the efficacy evaluation might be affected by Example 5.

All of the preceding examples had no documentation as to why the changes were made.

Then, how often do you hear from a data manager, statistician, project director, or your supervisor that:

- a. it is too late to open the database and you should make the correction(s), or
- b. the data change will not affect the overall safety or efficacy of the study so go ahead and make the changes, or
- c. if you document the changes in a program like README.SAS and keep a hard copy of the reasons why the changes are made, it is okay to it.

In the first case, it is never too late to open the database and make the correction. What the requestor is really telling you is that she or he cannot get all of the necessary signatures to open the database in a timely manner and project timelines will be affected. In reality, if timelines are affected by reopening the database and making the correction(s), then so be it. Wouldn't you rather delay the timelines than to compromise your standards?

In the second case, the data change(s) will not affect the safety or efficacy of the program. If that is the case, why not ask the medical writer to make such a comment in writing the report and to add the data element(s) in question to the errata list of the report.

The third case of documenting changes is particularly the most dangerous to everyone involved.

Two examples follow:

1. A programming manager working at a CRO had a client phone to ask for the return all of the data and programs written for a particular study that was completed about ten years prior. The data were relatively easy to restore from archive. The programs were easy to restore, but not that easy to select which were part of the production run. At the time that the study was active, there were no programming standards for program naming conventions or for detailing the production job stream.

There were many versions of what seemed to be the same production programs in the restored project library. If there had been a program that had code 'correcting' any of the data, the results would have been disastrous. Fortunately, the programming manager could not find any code in any of the programs that would have changed any values.

If there had been any programs that changed values and they had not been selected, then the "raw" data files would not have matched the CRF data.

2. A programmer was asked to programmatically change the data in the database to match the CRF. She dutifully made the change, documented it online in a README.SAS file and documented it in a study binder, as a hard copy. She thought that was enough to do to document her actions.

All was presumably well until it was time for the NDA. The programmer who made the change left the company and a new team was responsible for the NDA.

The program that had the change was not used for the NDA as the new programmer used one of his own style, never thinking that there would have been code in the program to change a data point. Well, when matching up the original tables for each study in the NDA with the new, pooled NDA table, the count was off. After a lot of research, the error of changing data programmatically was found.

In this case, the new NDA programmer never thought of checking documentation for this kind of programming change.

FEDERAL REGULATIONS

There are federal regulations concerning the issue of data quality and data integrity.

For INDs, 21 CFR 312.62(b) states that you must prepare and maintain adequate and accurate case histories; 21 CFR 312.68 permits the FDA to have access to and copy and verify any records or reports required under 312.62(b). For all other submissions, 21 CFR 11, effective on 2011-04-01, applies.

Case histories record all observations and other data pertinent to the investigation on each patient or subject administered the investigational drug or employed as a control. Case histories include Case Report Forms and supporting data.

21 CFR 11 applies to electronic records which are a combination of text, graphics, data, or other information in digital form, that are created, modified, maintained, archived, retrieved, or distributed by a computer system. The guidance also applies to any electronic record submitted to the FDA.

The agency (FDA) considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and equivalent to paper records and handwritten signatures.

The procedures and controls of electronic records include: validation, ability to generate accurate and complete copies of records suitable for inspection, review, and copying by the agency, protection of records to enable accurate retrieval, limiting system access, use of audit trails, system controls, and personnel training and experience. All of which are subject to inspection by the FDA.

COMPLIANCE

Compliance to these federal regulations is enforced by Compliance Program Guidance Manual, Chapter 52, Unapproved New Drugs, (7352.002) which was implemented on 2009-10-19."

The policy states "we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11."

Factors affecting regulatory action include:

1. Nature and extent of Part 11 deviation(s). FDA will consider Part 11 deviations to be more significant if those deviations are numerous, if the deviations make it difficult for the agency to audit or interpret data, or if the deviations undermine the integrity of the data or the electronic system. The FDA would have little confidence in data from companies that do not hold their employees accountable and responsible for actions taken under their electronic signatures.
2. Effect on product quality and data integrity. The FDA would consider the absence of an audit trail to be highly significant when there are data discrepancies and when individuals deny responsibility for record entries.
3. Adequacy and timeliness of planned corrective measures. Firms should have a reasonable timetable for promptly modifying any systems not in compliance (including legacy systems) to make them Part 11 compliant and should demonstrate progress in implementing their timetable. Requirements for procedural controls should be in place.
4. Compliance history of the establishment, especially with respect to data integrity. Deviations are considered more significant if a firm has a history of Part 11 violations or of inadequate or unreliable recordkeeping. Until firms attain full compliance with Part 11, FDA investigators will exercise greater vigilance to problems in complying with Part 11.

Regulatory Action Guidance states that program monitors and center compliance offices should be consulted prior to recommending regulatory action.

The FDA's Division of Bioresearch Monitoring Program (BIMO) is authorized to monitor the conduct and reporting of clinical trials to ensure that data from these trials meet the highest standards of quality and integrity.

CONCLUSION

I know that I don't look good in orange or stripes (prison uniform garb) or have a bottomless pit checkbook to cover monetary fines. How about you?

Now that you know that there are federal regulations and means of enforcement, you are in a position to refuse to programmatically change database data in order to have the data match what is on the Case Report Form or other data collection medium. You are in a position to have the data management group edit the data using their validated data management system.

You should program so that the FDA could walk in tomorrow to do a complete audit. Keep your programs neatly documented, keep your validation materials proving that your program works correctly with test data, and keep your programs clean. Let the data managers take care of data management. That is their responsibility.

REFERENCES

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FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials, 1999-04

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www.fda.gov

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