Data Quality
Why Do We Care?

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Data Quality and Accuracy

It is obvious that the data we review – clinical, CMC/drug quality, pharm-tox – must be real and accurate if it is to be informative, but what are we actually worried about?

1. It must not be made up; we need to know that real studies and measurements were done and recorded. There are usually records that support all this; lab data, protocols, and case reports, etc. There have been cases, however, where these measures were fabricated, sometimes easily detected (same EKG in successive weeks)
2. Accuracy and completeness. Sometimes a protocol identified measure (e.g., asking about sleep, appetite, suicidality, falls) may be omitted
3. Absence of bias in data collection or analysis, generally assured by blinding

But you need to know whether the rules were followed.

Data Collection

Consider clinical data generally recorded in case report forms increasingly electronic (not handwritten) and many sources

- Clinical endpoint – The investigator will directly ask about side effects and clinical endpoints often using protocol-specified queries or outcome scores. Others, lab technicians, sub investigators will obtain blood for lab tests, take BP, conduct ECGs, do stress tests or 6 minute walks, obtain PRO's. Do they follow plans and rules?

- Our issue is whether it is preformed optimally (6 minute walks, pulmonary function tests), and poor quality can induce "noise." Noise generally obscures effects, bad for sponsor regarding effectiveness, but not necessarily for safety. Measurements can be made up (BPs have been; the clue was that they were identical over time)

Possible Bias

We blind studies for very good reasons

Many endpoints and adverse effects are subjective. We don't want knowledge of treatment groups to affect either the findings of the presence of effects or quantitative assessment (scores).

- We therefore will want to know all details of blinding to treatment, and about the "firewalls" that prevent sharing this knowledge
- Treatments should look alike (capsules can be opened)
- How drug is assigned and how knowledge of assignment is hidden
- Side effects can reveal drug (hard to prevent but can have 3rd party do tests); e.g. person who does the exercise test is not person asking about adverse effects,

Later Opportunities for Bias

Trials are designed to protect against biased analysis. How to handle data is specified carefully; in protocol and SAP.

- How, if at all, patients can be removed from the study of analysis
- How study dropouts will be handled
- Exactly who knows patient assignment
- Who, it anyone besides the investigators, assesses endpoints
- Planned study endpoints, order of testing, specified analyses – all part of the SAP, which should be finalized before unblinding (and generally sooner)

A lot of what is important is illustrated by a long-ago experience that occurred well before we understood how a trail can be biased

The Anturane Reinfarction Trial (ART), late 1970s, taught us a lot.

Anturane Reinfarction Trial (ART)

Taught us about choosing primary endpoints up front, and then not changing them , and the risk of unplanned subsets

Taught us about intent-to-treat and accounting for all patients in analyses

Taught us about blinding results of interim evaluations, and using them to alter analytic plans, use of post-facto eligibility assessments and cause of death assessments, and use of cause of death assessments

ART (cont.)

The ART was in many respects a carefully conceived and designed trial. It was one of the first large outcome trials carried out by a drug company. Most outcome trials had been conducted by NIH or other U.S. or Foreign government agencies. It had several distinguished review panels to help design and analyze the trial. Nonetheless, it proved to be a model case of how bias can be introduced into a trail. And we do not know exactly how that happened. A critical analyst died in an auto accident as we were discovering the problems. The problems were:

- Changes in assessed study endpoints
- Late deletions of patients with endpoints that favored treatment
- Cause-specific mortality, a major endpoint, was assessed in a way that was not specified and greatly biased.

Late deletions/ineligibles

We don't always insist on ITT, but when events, e.g. fatal outcomes, that occur in patients on Rx are removed for any reason (compliance, eligibility), there is major cause for concern.

Obviously this is a particular problem (a fatal flaw) when people deciding on exclusion are not blind to Rx.

You need to know exactly who had access to unblinded data and who made all decisions about patient inclusion/exclusion, presence of endpoints, nature of endpoints (cause of death), etc.

History of ART

1975	(Sept). ART initiated. Sulfinpyrazone was a uricosuric drug that lengthened platelet survival and decreased platelet turnover. Interesting discussion of whether to count SD, as no effect expected (Anturane Reinfarction Trial), but decided to make all CV mortality the endpoint
1976(?)	Inquiry to IND about early stopping – seemed odd, given study blinded and on-going
1977	(July). All 1500+ entered; steering committee informed patients and interim result of 48.5% reduction in cardiac deaths (p=0.018 but not corrected), almost all due to 58% reduction in SD, at total follow-up average of 8.4 (months); (planned minimum=1 year)[Early assessment not necessarily unreasonable but not planned]
1978	Reobtained I.C., (no losses), continued trial to end (July 1978), published
1978	(Feb 9). NEJM report of study interim result with editorial

History (cont.)

1978 Filed NDA - Advisory Committee considered and said "not yet"; went for completion

1979 (March). Resubmitted NDA

1979 (Nov). CRAC recommended approval for prevention of SD in first 6 months after AMI, clearly NOT the planned study endpoint

1980 (Jan 31). NEJM Final report and supportive editorial

1980 (Mar). JR Crout tells Cardio-Renal to make a decision in 4 weeks (claim of decreased sudden death important) - it took 6 weeks

1980 (April). Review leads to non-approval

1980 (Dec 18). Temple and Pledger publication

Features of A.R.T.

Double-Blind (U.A. values hidden) -
Shipped from C-G with numbers.

Randomized in blocks of 10 within each clinic

Placebo-Controlled

Patient Population
- Male or female
- Age 45-70
- AMI 25-35 days before
- ECG Documentation
- Typical Pain History

Enzymes: 2 of CPK, SGOT, LDH had to exceed 2X normal - 72 hr

No cardiomegaly, CHF >NYHA II, life-limiting disease

Baseline co-variates
- Index MI and later symptoms
- Smoking
- Medications
- Chest x-ray

ART Results

The reported overall results were close to significant (but note that there was no suggestion of a "reinfarction" benefit)

A.R.T. REPORTED MORTALITY RESULTS

	Pl	S	% ↓ (p)
PATIENTS (Eligible)	783	775	
ALL DEATHS (analyzable)	62	44	29% (p=0.076)
CARDIAC D's	62	43	30.6 ~~32%~~ (p=0.058)
SUDDEN	37	22	43% (p=0.041)
AMI	18	17	--
OTHER	7	4	--
OTHER CV	0	1	--

MORTALITY by CAUSE, TIME

	Pl	S	% ↓ (p-value)
ALL CARDIAC	62	43	30.6% (p=0.058)
ALL CARDIAC			
0-6 M	35	17	50% (p=0.021)
7-24 M	27	26	
SUDDEN			
0-6 M	24	6	74% p=0.003)
7-24 M	13	16	
NON-SUDDEN			
0-6 M	11	11	
7-24 M	14	10	

Endpoints Presented (Protocol vague on all this, but plan was all CV mortality)

1. **Death** (All, CV)

2. **Kinds of Death**

   Sudden: within 60 minutes of sudden onset of symptoms, or unobserved, unless post-mortem showed AMI

   AMI: at least 2 of history, enzymes or ECG [problem; if not admitted to hospital, what do you call someone who dies after 61 minutes of chest pain (not sudden, not AMI unless P-M shows recent infarction); presumably "other"]

   No protocol guidance on interpreting post mortem findings

   Other: CHF, arrhythmias, acute coronary insufficiency (not defined)

   Possibly designed to include as AMI only sure things (i.e., reduce noise) because that is where effect was expected

Structure

Data sent to Ciba-Geigy; tried to catch exclusions (too old, too early after AMI) and exclude promptly. Whether this is a good idea is debatable, but if pre-event and blinded, impact would probably be small. Exclusion after an event is another matter.

Operating Committee - did initial review of deaths and cause of death assignments. Consultant John Tukey, Chair, Dept. of Stats at Princeton. NOT KNOWN IF/HOW BLINDED, or what data were used. There was no submission of this committee's cause of death assessment.

Policy Committee - distinguished academics (Sol Sherry). Said to be blinded.

Columbia - Quality Control, audits, etc.

J. Hopkins - comprehensive audit

Two main issues: 1) patient exclusions 2) cause of death analysis

Patient and Data Exclusions

Non-analyzable Data (Data leave the study); some clearly planned in advance

7-Day Rule (events on Rx < 7d; off > 7d) were excluded - controversial but not critical; reasons: no anti-platelet effect till 7 days; no effect after 7 days.

External causes - surgery unrelated to a non-fatal event on study

Exclusion because of poor compliance – not clearly planned;
specifically, not stated in protocol that their events would be excluded - final report listed 3 dead patients as non-analyzable (one already dead in 1978 report, but not mentioned as excluded). Medicine found in dead patients' room, obviously not taken.

Ineligible - patients mistakenly entered were dropped, as were poor compliers. One must distinguish early exclusion (i.e., before any event) vs. late exclusion (i.e., after event).

Issues

1. Blinding of Operations Committee (cause of death)

2. Cause of death assignment. Our documentation of basis for assignment stops at investigator, who seems not to have been involved in the final classification. Although there was a separate death form for each patient, describing the terminal event, but final assessments were often different. Not clear who made final assignment, who reviewed it, or whether the persons who did the assignment were blinded.

3. Procedure for review of eligibility; e.g., why would ineligibility be declared after death? And even if it were, what would justify late exclusion of patients in the study.

4. Exclusion of late discovered poor compliers who died. Note that there is evidence that poor compliance itself may be a risk factor. In Coronary Drug Project compliance predicted survival in both placebo and clofibrate groups. We would never allow exclusion of poor compliers after randomization.

Review

Results reported:

Near-significant reduction in total cardiac deaths, especially early

Highly "significant" reduction in early sudden death

Early not crazy:

1. Risk after an MI is greater early (but 6 month is arbitrary and was not prospectively specified)
2. Events early after AMI could be different from later events

SD not expected. Platelet sticking should cause AMI, not mostly SD. Again, Anturane REINFARCTION Trial

NEITHER RESULT ULTIMATELY SUPPORTED

- Cause of death analysis was biased
- Late exclusion drove favorable overall result, and 6 months result

Review (Post CRAC)

Cause of Death

Suspicion: NIH told us one patient had changed classification. How could that be?

Otherwise naïve; I had no idea that cause of death was so unstable. They never gave it a "trial run."

We looked at 50% of deaths, using a description of terminal event provided on a special form with each death, described (NB, the forms were 100% omitted in first submission. Initial submission used typed CRFs, not the original and the terminal event forms were omitted. Dr. John Harter demanded original handwritten CRFs. And the terminal event forms

We found misapplication of rules and inconsistency, generally tending to call a death on placebo sudden and a death on Anturane something else, even for very similar circumstances, leading to the strongest "findings", red.. sudden death on Anturane.

Cause of Death

We reviewed about 50% of all deaths, focusing, for obvious reasons, on early sudden deaths. Our review was not blind and was done by a single person (me). By the time this was done; it was clear that the 24 vs 6 (1st 6 months) significant SD finding was bogus. We had already reached 18 vs 11 after the 50% review and we concluded that the classification was unreliable. We did not try to redo it.

The following excerpts from the NA letter give more detail:

b. Audit of death classifications

We have carried out an approximately 50% audit of the analyzable deaths and have found numerous apparent misclassifications of the cause of death, nearly all favoring the hypothesis that Anturane prevents sudden death. While it is possible there is some reasonable explanation for many of the choices we consider erroneous, the basis for death classification decisions are nowhere explained or documented in the NDA filing. At a minimum, our analysis shows that the classifications are not at all straightforward. It is also striking that in the case of most sudden deaths, the local investigator thought recurrent infarction was the likely cause.

The classification errors were as follows (in this discussion the NDA classification is included in parentheses and "early" means within the first 6 months of the study):

(1) Classification as sudden death despite evidence of fresh occlusive thrombus or recent infarction at postmortem.

The NDA contains no guidelines for interpreting the results of postmortem examination, so that in some cases your reading may differ from ours. In the following cases, however, the diagnosis of recent infarction or occlusion seems reasonably plain:

1307-1 (early placebo sudden death)

Postmortem examination showed old and recent right coronary artery thrombosis.

1320-13 (late placebo sudden death)

Postmortem examination showed recent right coronary artery thrombosis.

1320-93 (late Anturane sudden death)

Autopsy says specifically that cause of death was acute thrombosis of right coronary artery.

1321-32 (early placebo sudden death)

Postmortem showed very recent extension of posterior septal infarction.

1321-45 (placebo late sudden death)

Autopsy showed “possible” very recent obstruction of the LAD artery.

1326-3 (placebo early sudden death)

Postmortem shows recent right coronary artery thrombosis in a patient with occluded LAD and left circumflex arteries.

1326-27 (Anturane early sudden death)

Postmortem showed old anteroseptal infarction with recent extension.

(2) Classification as sudden death despite history more compatible with a different diagnosis.

1316-26 (placebo early sudden death)

Patient had documented episodes of ventricular tachycardia (but refused hospitalization) for about one week before he collapsed after a dizzy spell. The cause of death is arrhythmia and symptoms of this arrhythmia preceded death by about a week.

1320-101 (placebo early sudden death)

Patient with mild angina (4 episodes in the week prior to death) developed 3 1/2 hours of pain characteristic of AMI and not relieved by nitroglycerin, then died abruptly. The local investigator did not consider this a death within 60 minutes of the onset of symptoms but considered the patient to have arrested after a recurrent infarction. This case seems best classified as "other cardiac" (using your rehospitalization criteria) or perhaps there needed to be a "possible AMI" category.

1321-22 (placebo early sudden death)

Similar to the previous case, this patient complained of chest pain for hours before death and used an unusually large number of nitroglycerin tables the night before. This does not meet the symptom-less-than 60 minutes criterion for sudden death.

1321-29 (Anturane late sudden death)

After 2 weeks of unstable angina the patient developed 1/2 hour of severe chest pain and died. This case conceivably meets the stated criteria for sudden death but almost surely represents an ischemic event; it does not seem very useful to treat it as different from a similar case in which a postmortem exam was performed and happened to show acute infarction (e.g., 1321-78) where very similar circumstances of death led to a designation of AMI because of autopsy findings).

1321-77 (placebo sudden death)

After dinner, the patient developed severe chest pain, fainted and died. Again, this may meet the stated criteria for sudden death but there was most likely a precipitating ischemic event.

1321-87 (placebo early sudden death)

The patient died about 2 hours after developing severe chest pain. Again, this probably was an ischemic event and symptoms were present for more than 60 minutes before death.

1325-11 (placebo early sudden death) and 1330-2 (Anturane late AMI)

These cases should be considered together because virtually identical circumstances led to different designations of cause of death.

Patient 1330-2 developed documented recurrent infarction on September 6, 1977 and did well until he was found dead in bed on October 2, 1977. Cause of death was given as AMI because death was considered related to the recurrent infarct. Death was so far after the infarct (26 days), it should be noted, that this patient could have entered the A.R.T. had he not been in it already.

Patient 1325-11 also had a documented recurrent infarction on April 3, 1976 with a fairly stormy hospital course, and died suddenly on April 23, 1976. This death, only 20 days post-infarction (i.e., would not have yet been eligible to enter the A.R.T.) was considered a sudden death and apparently was not considered related to the reinfarction. There seems little consistency to these decisions.

1330-4 (placebo early sudden death)

For several days before death this patient had increasing congestive heart failure, characterized by gurgling and choking. On the morning of death, he was seen to have jerking, stridorous breathing and died after a short while. This death most likely represented progressive congestive heart failure of several days duration, culminating in pulmonary edema.

Ineligibles and Non-Analyzable

As shown below, patients removed from the trial as "ineligible" (but after death), strongly favored Anturane. This non- analyzable had little effect

	Placebo	Sulf	p.value
Ineligibles			
ART, as presented, cardiac D's	62	43	0.058
poor compliance, ineligible	1	2	
ineligible (found PM)	0	6	
Total	63	51	>0.2
Non-Analyzable, < 7d			
Death < 7 days	5	4	
Death < 7 days, ineligible	1	0	
Total	69	55	0.2
Non-Analyzable, > 7d	13	10	
Grand Total	82	65	0.162

Late Exclusions

Strict ITT would be concerned about any late exclusions but ineligible and non-analyzable can be distinguished.

Non-analyzable were people not expected to benefit because they'd not been on drug long enough (< 7 days) or because drug effect was gone (>7days). Exclusion had modest effect, 5 on placebo, 4 on Anturane, favoring placebo somewhat.

Removing the "ineligibles", however, 1 placebo, 8 on Anturane, after they died was what made the result almost "significant" overall. And the removals were, to be blunt, ridiculous. Three were people found after death not to have taken drug. Six were people with concomitant illness, late entry (AMI > 35 days before) or other reasons and removal was post-event.

ART - Conclusions/Lessons

1. Cause of death analyses (cause-specific mortality) are treacherous, and out of the question if unblinded.

   We now:

   - have a bias toward all-cause or CV mortality
   - Often accept CV mortality (but without trying to distinguish further), esp where there are many non-CV deaths

2. Pay very close attention to the planned analysis, with great reluctance to look at time or outcome subsets not planned and not accounted for in statistical plan
3. Insist on full accounting of all randomized patients and an ITT analysis (even if sponsor prefers another). Somewhat controversial is inclusion <u>after</u> stopping drug; almost never done with symptomatic treatments. There is hardly ever a reason to drop someone still on treatment.