Objectivity vs competency in randomized trials

Objectivity in research is the product of methods and procedures in the study aimed at eliminating or minimizing the influence of subjective whim or arbitrary capriciousness on procedures or observations. The route to objectivity is via explicit rules and procedures as contained in protocols and study manuals and via constructs designed to eliminate or reduce the risk of subjective judgment.

Competency is a quality of a person or group of persons regarded as having the requisite skills, training, expertise, knowledge, and information necessary to ensure sound and proper actions.

The goal of the researcher is objectivity without compromising competency. But what about when the constructs imposed to achieve objectivity reduce competency? This talk is about that conflict in clinical trials.

So you want to do a randomized trial do you? Choose a couple of treatments, round up some people and randomize them to treatment. Then sit back and wait for the results to roll in, but always in the ready position to be first in line to author the results paper.

If only it was that simple. In reality, doing a trial is like performing a high wire act – without a net – and with a bevy of "shakers" at both ends of the wire. The trick is to making it across the wire.

Being able to venture out onto the wire at all, is itself, a privilege bestowed on us by a public willing to allow research on human beings. Everyone here is a beneficiary of that trust and, hence, we all have a duty to maintain it. Without that trust, we can board up places like this one.

The dilemma in all of clinical research lies in balancing risks against benefits while, at the same time, ensuring that the research is capable of producing "fruitful results for the good of society".

> *The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.* (2nd item in the Nüremberg Code)

What the "fruitful result" requirement means is that research, so poorly designed or conducted, so as to be incapable of bearing fruit is in and of itself unethical and a violation of the public trust, even if free of risk to persons studied.

For "*fruitful results for the good of society*", the trial has to be designed and conducted to yield valid treatment comparisons. To do that, comparisons have to be free of treatment-related bias. The route to bias-free comparisons in trials is via constructs and procedures aimed at reducing or eliminating bias. The usual constructs are those involving randomization, masking, and "shielding".

Largely, the view is that the credibility of a trial increases as a function of the number of objectivity constructs practiced. Trialists, therefore, strive for the highest level of objectivity. So when in doubt, they randomize and mask everything in sight. Double-masked treatment administration is preferred to single-masked administration, and single-masked administration is preferred to unmasked administration. In regard to shielding, generally, once the trial starts neither the patients nor those who care for them see interim results.

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No doubt, everyone in this room is familiar with the medical ethics principles of beneficence, respect for persons, and justice, enunciated in the Belmont report, but there is another principle, as important as these in trials, and that one has to do with competence. The principle of competency means that persons entering trials must be cared for in a safe and competent fashion by people with the training, skill, and expertise necessary to ensure safe and competent care. It means that the requirements of the study, as specified in the study protocol, must give way to requirements for safe and competent care when the needs of the study and those of study subjects are in conflict. In regard to objectivity vs competence, it means that study investigators are obliged to choose competency over objectivity when objectivity constructs reduce competency.

Elements of the requirement for competence are expressed in item 8 of the Nüremberg Code:
The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

They are seen, as well, in the 1993 World Medical Association Declaration of Helsinki:
Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

I should note in passing, that Richard Royall has addressed elements of this topic years back in this very room. His paper, "Ethics and statistics in randomized clinical trials" (with discussion) (Statistical Science: vol 6: 52-88; 1991) is a great read on what he calls the "personal care principle".

The "personal care principle" in trials means, not only that those doing the trial must come to it with the requisite training and expertise to ensure competency, but also that, during the trial, they must at all times be in possession of the requisite information and wherewithal to ensure safe and competent care. Operationally, the latter means that they may not be constrained by imposed objectivity constructs when they serve to reduce competency.

The most common objectivity design constructs in trials are randomization and masking. In terms of randomization, this means that it has to be limited to treatments consistent with the norms and standards for care. It means that the trialist cannot use a placebo as a control treatment if medical norms or standards dictate otherwise.

The choice of treatments in randomized trials is constrained by requirements of clinical equipoise. We cannot test treatments believed to be harmful.

Similarly, in regard to masking, the requirement means that, regardless of how desirable it may be from the perspective of the trial, it cannot be practiced if it carries risk for persons studied. It cannot be practiced if the mask reduces competency in caring for persons studied. The "work-around" when treatments are masked, is in having protocols with "bailouts" to allow unmasking or to require that study physicians stop treatment when in doubt regarding safety.

We can be reasonably sure that trials meet muster with the requirement for competency in regard to randomization and masking because they are part and parcel of the design and, hence, receive extensive review and scrutiny by investigators and IRBs before the trial is mounted. But

what about constructs imposed to shield investigators from interim results? Do they threaten competency? They most certainly can.

To appreciate this you need, first, to remember that harm in trials has two routes. One route, familiar to all, especially after 22 July 2001, is a direct consequence of something done to a study subject.

The other route is by failing to act. In the context of randomized trials, this form of harm accrues to a class of people as a result of continuing to receive a harmful or inferior treatment when results of the trial or other sources are sufficient to indicate there is a better treatment. This form of harm is avertable only if the results of the trial are routinely monitored and then only when there are mechanisms in place to stop or alter the trial when indicated.

The present day model is one in which investigators do not see interim results – sort of like a self-imposed frozen state of equipoise. The impetus for it came in the 70s from urgings of Tom Chalmers and others. It emerged largely as a dilemma-sparing expedient. The dilemma was due to pangs of conscience experienced by clinicians when faced with continued enrollment in the presence of encouraging trends in the trial.

He was joined in the push for shielding by people worried about treatment-related feedback bias. They argued that investigators involved in caring for people in a trial should not see interim results because knowledge of results of the trial might bias their actions.

Another argument for "shielding" had to do with "conflicts of interest". People argued that investigators, if allowed to monitor might be inclined to stop with the first hint of a positive trend. Others argued that they might be disposed to continue to the bitter end, regardless of the results, to maintain funding.

The "solution" was to move responsibility for monitoring from study investigators to an "independent" body remote from study investigators.

Having been removed from the monitoring process, it was only a matter of time before investigators lost control of monitoring. Control shifted, inexorably, starting in the late 70s, to sponsors – a transition, no doubt, accelerated by the advent of government initiated trials via RFAs and RFPs.

That shift of control is at odds with ethical codes underlying research. They indicate that the duty to protect and care for study subjects is an inalienable duty of those who do the studying, not transferrable to parties remote from the study. But no one seems to have noticed or to care. Even the ethicists, have been strangely silent on this transfer. And IRBs have been of no help. Indeed, I might even go so far as to say that they have been part of the problem.

Incidentally, lest you think I am too hard on IRBs, I should note that the problem with IRBs, when it comes to multicenter trials, lies in the name *Institutional Review Board*. In multicenter trials, there are dozens of IRBs involved, all autonomous, all equal to one another. There is no supreme IRB. There is no IRB concerned with the entire trial. The best that can be hoped is that the various pieces represented in the different submissions add up to the whole. But do they? Not when it comes to monitoring. Basically every IRB is content to leave the nitty gritty issues of how monitoring is done to some "other IRB".

IRBs have the power to level the playing field with sponsors in regard to monitoring, but I see no sign of that happening. Indeed, the cynic in me leads me to conclude that IRBs are too busy word-smithing consents and making certain that we do not bank ill-begotten specimens to be concerned with whether investigators are in charge of their own studies.

We should be concerned regarding the transition, if we believe, as I do, that an informed and involved investigatorship is the best protection patients have. Removing investigators from monitoring relegates them to the potted plant stage of activity and potted plants are not in the best interest of persons studied. We delude ourselves if we think IRBs are the prime protector of study subjects. Their best protection is via informed investigators.

We should also be concerned as scientists because the removal marginalizes the role and function of investigators. Can anyone here name another branch of scientific investigation where those who do the research are not trusted to see the data they collect? Is it not strange that for one of the riskiest forms of clinical research that we are content in excluding those who know the most about the study and treatments from the monitoring table?

The concern now, with the investigators neutralized and with IRBs asleep at the switch, is the absence of checks to make certain that the desire for objectivity does not supersede the need for competency.

The typical objectivity constructs in regard to treatment effects monitoring include the following:

- P-value based pre-ordained stopping rules
- "Look" restrictions; re number of "looks" allowed and on what can be "looked" at
- Masked analysts
- Coded monitoring reports
- Firewall separation in the coordinating center to keep the Director and other key CC leaders from seeing interim results; especially when seated on the study steering committee
- TEMC masked to treatment assignment
- TEMC voting members not associated with the trial
- TEMC study representatives limited to those not having treatment responsibilities in the trial
- TEMC votes on recommendations regarding the trial cast in closed executive sessions
- TEMC members appointed without knowledge or consent of investigators
- TEMC commissioned to report to sponsor

The issue of competence in monitoring would be largely irrelevant if trials, from beginning to end, covered only a short time span, but the reality is that it can take years to enroll and years more to finish treatment.

So who is watching the store in regard to monitoring? Treatment effect monitoring committees (also Data and Safety Monitoring Committees (DSMC) or simply Data Monitoring Committee (DMC)), bodies, incidentally, not accountable to any IRB and often, at least for NIH-sponsored multicenter trials, appointed by the NIH and accountable to the NIH and NIH alone.

So now the Mother of the Mother Test questions: Would you enroll your Mother in a trial where the investigators are masked and barred from seeing interim results, where analysts are

masked, where the TEMC is masked, and where it reports to the sponsor? Not my Mother, rest her soul! How about yours?

The irony is that these constructs are imposed to "protect" the trial. What about the patients?

So what you ask? What is the harm? Because they constrain and restrict in ways that have the potential to increase risk to persons studied.

Consider stopping rules and restrictions on the number of looks. Those restrictions are good for p-values but not for competency in monitoring. I know I would have trouble explaining to my Mother why looking at data is bad. I just know that she would ask if I was dumb enough to believe that data can be spoiled by looking at them! And I am as certain as I can be that she would throw me out of the house if I tried to tell her that one should ignore bad effects because planners did not have the foresight to construct a rule for that outcome. What would you rather have? A protected Mother or protected p-values?

What about masked monitoring? Again, desirable from the point of view of the trial, but what expense to competency? If you think masked monitoring is a good idea, then you need to sit on a masked monitoring committee. The reasons to steer clear of masking have been set forth in an article in the NEJM in 1998 entitled *Masked monitoring in clinical trials – Blind stupidity?*

Masked monitoring is predicated on a fallacious assumption, namely that decision making in trials is symmetrical about the line of no treatment difference. It is not! If a difference emerges you need to know the sign of the difference to decide whether or not to act. Typically, one stops well short of "significance" if the trend is in the wrong direction. Largely, to be competent in analyzing data, one has to know treatment group.

How about enrolling your Mother into a trial where people in charge of the data and analysis are masked? The masking deprives the analyst access to the most important variable in the trial – treatment assignment – and in so doing deprives the analyst of the means to check for coding errors re treatment assignment. More blind stupidity?

And is your Mother better off by being part of a study in which the director of the coordinating center is barred from seeing data? Hardly as soon as one realizes that such firewalls virtually eliminate any role for the Director in supervising analyses or in quality assurance in regard to analysis processes.

But probably the most debilitating constructs imposed on TEMCs have to do those aimed at insulating the TEMC from study investigators. I am old enough to have been around when investigators did their own monitoring. The Steering Committee in the UGDP (University Group Diabetes Program) was responsible for monitoring. It was responsible for the decision to stop use of tolbutamide in the trial and also, later on, responsible for stopping use of phenformin when those drugs were found to be no better and perhaps worse than placebo. I seriously doubt that our respective Mothers are better today by being in trials comprised of monitoring bodies devoid of enrolling and treating investigators.

The argument for their exclusion has to do with worries concerning treatment-related feedback bias and "conflicts of interest".

But, the risk of treatment-related feedback is nonexistent in masked trials and largely trivial in unmasked trials with "hard" outcomes. And as to "conflicts of interest", only Alfred E Newman is free of them. It is foolish to assume that just because members of TEMCs are remote from the trial, that they are, therefore, free of conflicts of interest in regard to decisions.

There can be no doubt that those involved in conducting the trial have the most intimate knowledge of the protocol, of the data collection procedures, and of the treatment protocol. That knowledge is of paramount importance in understanding and explaining treatment results. To deny the monitoring body that level of expertise is to render the body incompetent whenever it is forced to "guess" as how data are collected or details of the treatment protocol because they have chosen to isolate themselves from study investigators.

Sooner or later this march to oblivion via objectivity has to stop. One day, somewhere, a trial will go too long because the TEMC was masked or otherwise constrained and then, all of sudden, things will change and IRBs will start making demands they should have been making years ago. That day cannot come too soon for me as a trialist and as a human being concerned about what we are willing to do to our Mothers in trials in the name of contrived objectivity.

(Sunday) 2 February 2003

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Objectivity vs Competency in Randomized Trials

Biostatistics Grand Rounds

Wednesday 5 February 2003

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Baltimore, Maryland
The Johns Hopkins University
Bloomberg School of Public Health
Center for Clinical Trials

Objectivity vs competency in randomized trials

Generation time and date: (Sunday 7:54am) 2 February 2003; Location: \BioGrand

Objectivity vs competency in randomized trials

Objective/competent

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objective *n* - Uninfluenced by emotion, surmise, personal prejudice, or bias; not subjective.

competent *adj* - Having the requisite skills, abilities, and qualities sufficient to allow one to perform up to some standard or level

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Objectivity vs competency in randomized trials

Objectivity

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objectivity *n* - The state or quality of being objective; in research achieved by written rules, procedures, and constructs designed to reduce room for subjective judgment

objectivity construct *n* - [trials] A construct imposed to reduce potential for treatment-related bias typically via randomization, masking, or shielding

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Objectivity vs competency in randomized trials

Objectivity constructs

- Randomization
- Masking
- Shielding

Objectivity vs competency in randomized trials

Objectivity vs competency in trials

Fact 1: Most objectivity constructs have potential for reducing competency
Fact 2: Need for competency must supersede need for objectivity
Fact 3: The tendency is to impose objectivity constructs assuming on effect on competency

Objectivity vs competency in randomized trials

Item 2 of the Nüremberg Code

The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature

Objectivity vs competency in randomized trials

The principle of competence

A principle in medical ethics asserting that the care and treatment offered to research subjects must be consistent with accepted standards of care and treatment and that such care and treatment must be offered and applied in a competent fashion by people having the requisite skills, expertise, information, knowledge, and wherewithal necessary to ensure competence

Objectivity vs competency in randomized trials

Item 8 of the Nüremberg Code

The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment

Objectivity vs competency in randomized trials

Treatment effects monitoring

In trials, the act of or an instance of reviewing accumulated outcome data by treatment group to determine if the trial should continue unaltered.

Objectivity vs competency in randomized trials

Treatment effects monitoring

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treatment effects monitoring committee (TEMC) *n* - [trials] A standing committee in the structure of trials responsible for the periodic review of accumulated data for evidence of adverse or beneficial treatment effects and for making recommendations for modification of a the trial based on accumulating data. syn: data monitoring committee, data and safety monitoring committee, safety monitoring committee

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Objectivity vs competency in randomized trials

Design objectivity constructs

- Randomization
- Masked treatment administration

Objectivity vs competency in randomized trials

The shielding construct

The act or process of keeping designated groups of people from seeing interim results, eg, investigators during conduct of the trial; accomplished by blackout of results by treatment group

Objectivity vs competency in randomized trials

Monitoring objectivity constructs

- P-value-based pre-ordained stopping rules
- "Look" restrictions; re number of "looks" allowed and on what can be "looked" at
- Masked analysts
- Firewall separation in the coordinating center to keep the CC Director and other key CC personnel from seeing interim results; especially any such person seated on the study steering committee
- TEMC masked
- TEMC voting members not associated with the trial
- TEMC study representatives limited to those not having treatment responsibilities in the trial
- TEMC votes and deliberations in closed executive sessions
- TEMC members appointed by sponsor
- TEMC commissioned to report to sponsor

Objectivity vs competency in randomized trials

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Objectivity vs competency in randomized trials

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