INTERVENTION, FOLLOW-UP AND PROTOCOL ADHERENCE

From the Therapy chapter for the 3rd edition of Clinical Epidemiology, by DL Sackett
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Intervention, Follow-Up and Adherence Check List:

1 ❍	Based on your trial's question, specify the precise experimental and comparison regimens.
2 ❍	Identify a source for the regimens and, if you plan to blind the patients and/or clinicians, ensure that they and their containers are indistinguishable.
3 ❍	Set up a system for distributing and maintaining supplies of the regimens.
4 ❍	When patients and/or clinicians are blind, set up a system for emergency code-breaking.
5 ❍	When patients and/or clinicians are blind, set up systems for maintaining blindness.
6 ❍	Decide what to do about monitoring (and, if necessary, improving) patient compliance.
7 ❍	Set up a system for avoiding (and documenting) contamination and co-intervention
8 ❍	Based on your trial's question, design the follow-up procedures.
9 ❍	Set up a system for monitoring (and, if necessary, improving) protocol adherence by study clinicians and staff.

We randomized study patients to one of four oral regimens. Each was taken 4 times daily and consisted of either: a 200 mg tablet of sulfinpyrazone plus a placebo capsule; a placebo tablet plus a 325 mg capsule of acetylsalicylic acid; both active drugs, or both placebos (the manufacturer of sulfinpyrazone supplied both the active drugs and placebos). Each active drug and its corresponding placebo were identical in size, shape, weight and color and were shipped to the participating centers in identical bottles of 130, labeled with 4-digit random numbers. Neither the patient nor their clinician were told which regimen had been assigned, but both were given a 24-hour telephone number for emergency code-breaking. To prevent participating neurologists from inadvertently breaking the code by discovering the hypouricemia that sulfinpyrazone produces, local laboratories deleted uric acid values from their local reports and sent them directly to the Methods Center. At the end of the trial (but before the code was broken), we asked the neurologists to predict both the overall study results and the regimens for each of their patients.

We asked our patients to return unused medication at each follow-up visit, and we counted their remaining pills counted to estimate medication compliance. We also measured compliance, contamination and co-intervention by determining changes in serum uric acid, sulfinpyrazone blood levels, and aspirin-specific in vitro effects on platelet function (keeping all of these results from patients and their neurologists throughout the trial). Because of the ubiquity of aspirin-containing compound, we urged our patients to avoid cold remedies and other over-the-counter nostrums, and recommended acetaminophen (paracetamol) when an analgesic was needed. Finally, because many psychoactive drugs also affect platelet function, we asked study patients' clinicians to restrict their choice of tranquilizers to diazepam or chlordiazepoxide.

We re-evaluated study patients at 1 and 3 months and every 3 months thereafter. At each visit we obtained a detailed neurologic history and examination, smoking history, blood chemistries, hematological measurements, and platelet function tests (we repeated chest films and electrocardiograms annually).At the end of each visit, study staff telephoned the Methods Center and the next bottle of study drugs was assigned.

The scenario chronicles how we handled the items on the check-list, and contains one glaring error (see if you can spot it before we get to it below).

1. **Based on your trial's question, specify the precise experimental and comparison regimens.**

You should begin by deciding who should do what to your study patients, and when and where this should take place. As with every other item on the intervention check-list, whether your decisions here are "right" and "wrong" will depend less on some absolute methodological imperatives than on how well they match your study question's location along the explanatory – management spectrum. Consistent with the highly explanatory nature of the RRPCE study, expert stroke-neurologists applied its specially-prepared treatments in a double-blind fashion during frequent patient-visits to the sub-specialty clinics of major university-affiliated hospitals. This specification would have been inappropriate for an extremely pragmatic trial of these drugs. In the latter case, we'd recruit general practitioners into a trial of open label aspirin vs. nothing, carried out in routine office practice.

We will discuss placebos a lot in the next section (page xx) of this chapter and, as pointed out there, they can be formulated as mock procedures or non-therapeutic patient-clinician interactions as well as by dummy pills. It often is either impossible or unethical to devise mock-procedures in surgical trials. For example, in our RCT of extracranial-intracranial anastomosis for threatened stroke we never even discussed drilling unnecessary burr holes and carrying out "mock" superficial temporal – middle cerebral artery anastomoses[1]. On the other hand, a group of Texas-based investigators, with approval from their ethics committee, carried out skin incisions and simulated debridement of knee joints in the "placebo" group of their RCT of arthroscopic surgery for osteoarthritic knees[2]. It's a good thing that they did, because they wound up ruling out any important difference in pain and function following the full and mock procedures.

When the application of experimental treatments to study patients requires patients to spend significant time with those who treat them, it may become difficult to distinguish the effects of what transpires during that time together (psychotherapy, skills training, and the like) from the simple effect of the attention they've received during that process. If this is an issue in your RCT, you might consider introducing an "attention-placebo" in which control patients spend an identical amount of time with their therapists, but receive none of the experimental "active ingredient" along the way. For example, a group of psychologists in North Carolina wanted to see whether a specific maneuver ("eye movement desensitization and reprocessing" or EMDR) would reduce the suffering of patients with whose panic disorders included agoraphobia (the fear of open spaces and public places)[3]. They randomized patients currently on their waiting list for desensitization and reprocessing to three regimens: immediate EMDR, remaining on the waiting list, or an immediate attention placebo consisting of relaxation training plus "association" therapy. They found that patients undergoing immediate EMDR had less severe symptoms on follow-up than patients randomized to remain on the waiting list. However, EMDR patients fared no better than patients who received attention placebos, and the authors concluded "EMDR should not be the first-line treatment for this disorder."

When should you stop using placebos? This is discussed in some detail in the following section on "placebo ethics." For now, we'll simply state that we stop using placeboes as soon as the results of RCTs (better still, systematic reviews of RCTs) convince the "expert clinical community" that an experimental treatment does more good than harm. By the reduction of this uncertainty (which could also be described a loss of clinical equipoise), the previously experimental treatments becomes "established-effective-therapy." As soon as an effective therapy is established, we don't think it is either ethical or clinically sensible to test the next promising intervention against placebo (this principle isn't pertinent when patients can't or won't take the established-effective-therapy, nor when the next promising treatment can't be added to it, as we'll describe in a minute). But if our conviction confuses, offends, or excites you too much, you might want to jump ahead to "placebo ethics" right now.

Suppose you think that the new treatment you are testing in your trial might provide further benefit to patients when it is given in addition to established-effective-therapy. In that case, you can determine its "superiority" or incremental benefit by specifying your control group as established-effective-therapy alone, and your experimental group as established-effective-therapy plus the new treatment. For example, by the time the post-myocardial infarction statin trials were carried out, previous RCTs of beta-blockers, aspirin, and several other drugs had established them as effective therapy for this condition. These later statin trials therefore compared these established-effective-therapies alone (the control group) with an experimental group receiving both the established-effective-therapies and a statin. When drug trials of this sort need to be carried out in a blind fashion, control patients are given established-effective-therapy plus placebos, resulting in what is often called an "add-on" trial. The key issue here, however, is that all patients in both groups receive EET.

Suppose, on the other hand, that you are not testing an "add-on" to be given at the same time as established-effective-therapy (say it's a new antiplatelet drug that, for safety reasons, can't be given with aspirin). In this case, it's both sensible and ethical to specify your treatment groups as established-effective-therapy (control) vs. the new treatment (experimental). Because such "head-to-head" trials withhold established-effective-therapy from the new treatment group, you need plenty of prior evidence (from bench research and Phase 1 and 2 trials) to justify withholding it. Ideally, this prior evidence will strongly suggest that your new treatment is better than established-effective-therapy. Alternatively, it should strongly suggest that your new treatment is as good as established-effective-therapy, but possessing some other advantage such as being safer, cheaper, easier to take, or the like.

2. **Identify a source for the regimens and, if you plan to blind the patients and/or clinicians, ensure that they and their containers are indistinguishable.**

As in the RRPCE study, it usually is relatively easy to obtain free active drugs and indistinguishable placebos from drug manufacturers, especially when the latter stand to gain financially from a positive trial. Clearly, the time for you to test their indistinguishability is before, not during, your trial. You want to be sure, before you begin, that they look, taste, smell, feel, and float the same.
Next, you need to be sure that the unblinding of one patient does not unblind any other patients (as would occur if, as in one study we know about, all active containers were labeled "Treatment A" and had black caps and all placebo containers were labelled "Treatment B" and had white caps). "Mock procedure" and "attention" placebos need attention of a rather different sort. The objective there is consistency in applying the mock procedure or attention to every control patient.

3. **Set up a system for distributing and maintaining supplies of the regimens.**

Mundane but crucial, you need to be sure that every center has enough of the experimental and control regimen at hand to meet the needs of every new and follow-up patient. Overnight couriers can get you out of trouble, but they eat up your budget.

4. **When patients and/or clinicians are blind, set up a system for emergency code-breaking.**

Patients and their clinicians must have 24/7 access to an emergency code-breaking service. When this service is supplied by the local center's pharmacy, code-breaking may occur for trivial reasons. When feasible, we prefer to provide a central code-breaking service that can study and discuss each specific request. As a general rule, if the subsequent management of a patient who stops the study drug for any reason would be the same whether they were on the experimental or control regimens, there is no reason for breaking the code. This policy is especially important if

the patient is likely to resume taking the study drug at some later date. Among the 585 patients in the RRPCE trial, we broke the code for just 1.

5. When patients and/or clinicians are blind, set up systems for maintaining blindness.

Systems for maintaining blindness begin with the provision of identically-appearing active and control treatments. This is easy when both are pills, but can be difficult for non-drug regimens. You've already learned (page xx) how a surgical trial maintained blindness by performing incisions on both groups. The most intricate I've encountered was a trial on the question: "Among in-patients with proximal vein thrombosis, does a continuous heparin infusion (compared with intermittent subcutaneous heparin) reduce the risk of recurrent venous thromboembolism?[4]" Because the search for outcome-events included clinical suspicion as well as routine surveillance, blinding was vital. We solved this by giving every study patient both an infusion and subcutaneous injections, only one of which was real and the other a placebo (some trialists call this a "double-dummy" strategy). We even gave the ward staff regular instructions to change the doses of both the active and placebo regimens.

In some trials, you will need to blind patients and clinicians to tell-tale "markers" of their treatments as well as to the treatments themselves. As you learned in the scenario, one of the drugs in the RRPCE trial caused a fall in the serum uric acid results that were included in most routine laboratory reports. Special arrangements had to be made with each laboratory to delete these values from routine reports and send them only to the methods center (see item 6 below).

Should you test for blindness during and after your trial?

Should you continue to test for the maintenance of blindness throughout and after your RCT? Although we urge that such tests be routine and rigorous before the trial, as the regimens are being created and debugged, we think testing for blindness should stop there. Our reasons are two. First, we don't want to create a "guessing game" environment during the trial that might render patients and clinicians more interested in guessing their regimen than in following it.

Second, we learned the hard way that "end-of-study" tests for blindness don't really test for blindness (and this is the mistake we alluded to at the start of this section). As noted in the scenario, at the end of the RRPCE trial, but before its results were given to them, study neurologists completed forms in which they predicted both the overall study results and the regimens for each of their patients. With 4 regimens, we'd expect blind clinicians to guess the correct one for 25% of their patients. We held our breath, hoping that our clinicians wouldn't do better than this, for fear that their "loss of blindness" would damage the credibility of our trial. As it happened, they did statistically significantly worse than chance, correctly identifying the regimen for only 18% of their patients! Our faulty reasoning was exposed when we examined their predictions of the overall study results: they tended to predict that sulfinpyrazone was efficacious and aspirin wasn't, precisely the reverse of the actual result. It then dawned on us that we were testing them, not for blindness, but for their hunches about efficacy. When their patient had done well they tended to predict they were on sulfinpyrazone, and when they had done poorly, on placebo or aspirin. How fortunate for us all that their hunches were wrong. If they had been correct, the interpretation of our end-of-study test for blindness would be that they had broken the randomization code. We hope that future trialists won't repeat our mistake.

6. **Decide what to do about monitoring (and, if necessary, improving) compliance.**

Sometimes you can make a case for omitting ongoing compliance monitoring. For one-shot treatments (operations and the like), compliance monitoring is complete at the start of the trial. In management trials that are testing alternative treatment policies for their real-world effectiveness,

you can argue that you should leave patients alone to comply or not as they would if no trial were underway. Even in this latter case, however, readers of your subsequent report will wonder whether study patients followed their assigned regimens. Accordingly, you should consider setting up unobtrusive compliance measurements even in the most pragmatic of trials. These could include monitoring (but not feeding back to patients or clinicians) the extent to which the former kept follow-up appointments, refilled prescriptions, and the like.

It is in performing explanatory (efficacy) trials of repeated or long-term treatments that compliance monitoring and intervention are important. Because your explanatory trial's objective is to show whether your experimental treatment can work under ideal circumstances, you want to be sure that study patients are complying with it. One way to achieve high compliance is to identify and exclude noncompliers before the trial begins. For example, the US Veterans Administration landmark hypertension trials in the 1960's placed all prospective study patents on a riboflavin-laced placebo and gave them a set of clinic appointments, at each of which their urines were tested for riboflavin[5]. Only patients who kept their appointments and consistently passed riboflavin were eligible to be randomized.

If such a "faintness-of-heart" strategy is not feasible, you will have to decide how to detect the different forms of noncompliance and what to do when you find them. We've summarized some advice about this in Table 07-01.

Table 07-01: Types of noncompliance and what to do about them:

Type of noncompliance	Detection	Strategy for preventing or improving
Dropping-out	Stops attending to renew study drugs.	Transport, home visits, or at least keeping in touch.
Stopping study treatment	Returning full containers	Negotiation
Missing follow-up visits	Partial attendance	Home visits
Low compliance with study treatment	Interviews, pill-counts, electronic pill containers, body fluid measurements.	Behavioral strategies, including feedback and incentives.

You should contact patients who drop-out of your trial and, unless they wish to be left alone, identify the problems that caused this. You can then negotiate solutions to these problems with them (transport to and from the study center, more convenient visits, home visits for delivering study drugs and monitoring progress, etc). Study patients who miss occasional follow-up visits may accept home visits. When patients keep their appointments but return full containers or aren't following any of their assigned treatment, problem-solving and negotiation should center on gaining their willingness to take at least some of it. If sensible given their regimen, "drug holidays" can be negotiated, followed by resuming all or at least some of their assigned treatment.

The most common problem for most trials is low compliance with study regimens among otherwise cooperative study patients. The cold hard fact is that people who are prescribed self-administered medications in routine clinical practice typically take less than half of their prescribed doses[6]. In RCTs, however, compliance as measured by pill-counts is usually high (92% in the RRPCE trial). This may be due to the increased attention, information, and supervision trial patients receive. The methods for detecting low compliance, ranked from easiest

(but least sensitive) to hardest (but most sensitive) are: asking the patient, counting returned pills, employing electronic pill containers that record whenever they are opened, and (for the most accurate determination of compliance on the day of measurement) determinations of drugs or their metabolites in body fluids.

Once detected, what can be done to improve study patients' compliance with their treatments? Effective strategies identified so far tend to be rather weak, and must be combined and sustained to be helpful. They are combinations of: more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, and other forms of additional supervision by or attention from a health care provider (physician, nurse, pharmacist or other)[7]. We suggest that you periodically consult The Cochrane Library to keep abreast of updated systematic reviews about effective compliance-improving strategies.

7. <u>Based on your trial's question, design the follow-up procedures</u>.

If yours is a pragmatic trial involving "hard" outcomes like death, you may plan for no follow-up visits at all, just an end-of-study determination of study patients' outcomes. At the other extreme, an explanatory trial may require frequent follow-up visits and extra attention that would not be provided in ordinary care (in the RRPCE trial we asked patients to come in every 3 months regardless of how they felt they were doing).

How frequently to schedule follow-up visits in an RCT is a balancing act. On the one hand, the increased cost, bother, investigator and patient fatigue, and opportunities for lost or incomplete data all argue against frequent follow-up visits. On the other hand, the need to search for and respond to side-effects, the attention required for maintaining high compliance, the need to detect subtle or intermittent outcome events, and the simple necessity for keeping track of study patients may require frequent visits. Blind trials always require identical follow-up schedules for experimental and control patients. Moreover, when outcome-events are mild (fatigue) or "soft" (fleeting sensory transient ischemic attacks), identical follow-up schedules for experimental and control patients will detect them with equal accuracy.

In any case, you want to keep track of every patient in your trial. You laid the groundwork for this by gaining contact information for the patient's younger relative at the time of recruitment, and in long term trials you may need to update this information periodically. With care at the outset and effort along the way, it is possible to keep track of virtually every patient in your trial (we lost 1% of our RRPCE patients, but none of 1495 in the EC-IC Bypass Trial and none of 662 patients in the NASCET trial).

8. <u>Set up a system for avoiding (and documenting) contamination and co-intervention</u>.

You don't want control patients to accidentally (even worse, intentionally) receive the experimental regimen (contamination). This is easy when the experimental regimen is available only within the trial. But when it is available outside the trial you will need to ask patients and study clinicians to avoid it and to use alternative drugs when required. For example, in the RRPCE we asked all study patients to avoid aspirin and other platelet-suppressing drugs, recommending acetaminophen for pain. We monitored aspirin contamination in several centers with a platelet function test specifically affected by aspirin, and sulfinpyrazone contamination with a review of serum urate levels (which are lowered by sulfinpyrazone).

Similarly, you don't want just one of your groups to receive some additional intervention that might affect their risk of an outcome-event (co-intervention). When it is possible to keep patients and their clinicians blind to their treatments, this is not a concern. When blinding is impossible or unwarranted, you might ask study clinicians to generate consensus-protocols for all other

treatments, including interventions for frequent or perplexing co-morbid conditions, in both groups.

9. **Set up a system for monitoring (and, if necessary, improving) protocol adherence by study clinicians and staff.**

We've already described some of the elements of this system (monitoring code-breaking, patient compliance, contamination and co-intervention). You'll want to monitor the timeliness with which follow-up visits are held and reported, as well as the quality and timeliness of the data submitted in these reports. The speedy detection and intervention around protocol violations is important, and although some of this work can be carried out by study staff, one of the most important functions of the Principal Investigator (and a high priority for their time and talents) is to go out to centers with flagging adherence and help them improve their performance.

Once again The Cochrane Library can provide the trialist with promising strategies that have been shown to improve the rates with which clinicians apply clinical protocols. Chief among these strategies is audit and feedback[8], with marginal additional improvements from interactive (not merely didactic) workshops[9], and educational outreach visits, particularly when "educational influentials" apply "social marketing" strategies[10].

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