Chapter 14
Participant Adherence

The terms compliance and adherence are often used interchangeably. In 1979, Haynes et al., defined compliance as "the extent to which a person's behavior (in terms of taking medications, following diets or executing lifestyle changes) coincides with medical or health advice" [1]. More recently, an international consensus statement crafted by the World Health Organization and the International Society of Pharmacoeconomics and Outcomes Research defined medication adherence as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime" [2]. Patient adherence is also recently reviewed in additional articles [3–5]. The term adherence implies active participant involvement in the decision to take a medication, use a device or engage in a behavior change, and is the term used in this book. In this chapter, we primarily refer to drug adherence but the concepts apply generally. In a drug trial, adherence typically refers to ingestion of predetermined amount of drug such as 80% of the protocol dose. This dose will depend on the nature and half-life of the drug being evaluated. Persistence is a related term that refers to remaining on a medical treatment for a specified period of time, regardless of the proportion of the doses taken. Distinguishing adherence vs. persistence is important since the metrics are different as well as the implications for trial interpretation [6, 7].

Medication adherence is a major challenge for patients, the consequences of which affect clinical practitioners and investigators alike. As many as one-third of all prescriptions are reportedly never filled and, among those filled, a large proportion is associated with incorrect administration [8]. Even among patients who receive medication at no cost from their health plans, rates of nonadherence reach nearly 40% [9]. Nonadherence has been estimated to cause nearly 125,000 deaths per year in the U.S. and has been linked to 10% of hospital admissions and 23% of nursing home admissions [8]. Poor medication adherence in the U.S. has a resultant cost of approximately $100 billion a year [10].

This chapter discusses what can be done before enrollment to reduce future adherence problems, how to maintain good adherence during a trial, how to monitor adherence, and how to address low adherence. In the monitoring section, we also

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discuss visit adherence. Readers interested in a more detailed discussion of various adherence issues are referred to an excellent text [11] and a review of the literature [10].

Fundamental Point

Many potential adherence problems can be prevented or minimized before participant enrollment. Once a participant is enrolled, measures to monitor and enhance participant adherence are essential.

Definitions

Since reduced adherence with the intervention has a major impact on the power of a trial, realistic estimates of cross-overs, drop-ins and drop-outs must be used in calculating the sample size. Underestimates are common and lead to underpowered trials that fail to test the trial hypotheses properly. See Chap. 8 for further discussion of the sample size implications of low adherence.

A *cross-over* is a participant who, although assigned to the control group, follows the intervention regimen; or a participant who, assigned to an intervention group, follows either the control regimen or the regimen of another intervention group when more than one intervention is being evaluated. A *drop-in* is a special kind of cross-over. In particular, the drop-in is unidirectional, referring to a person who was assigned to the control group but begins following the intervention regimen. A *drop-out* is also unidirectional and refers to a person assigned to an intervention group who fails to adhere to the intervention regimen. If the control group is either on placebo or on no standard intervention or therapy, as is the case in many superiority trials, then the drop-out is equivalent to a cross-over. However, if the control group is assigned to an alternative therapy, as is the case in noninferiority or comparative effectiveness trials, then a drop-out from an intervention group does not necessarily begin following the control regimen. Moreover, in this circumstance, there may also be a drop-out from the control group. Participants who are unwilling or unable to return for follow-up visits represent another type of low adherence, sometimes also referred to as drop-outs. Because of the possible confusion in meanings, this text will limit the term drop-out to mean the previously defined adherence-related behavior. Those who stop participating in a trial and have no further follow-up will be referred to as *withdrawals*. Importantly, participants who stop taking their study medication but continue their scheduled follow-up are not withdrawals.

Medication Adherence

The optimal trial from an adherence point of view is one in which the investigator has total control over the participant, the administration of the intervention regimen, which may be a drug, diet, exercise, or other intervention, and follow-up. That situation can only realistically be achieved in animal experiments. Any clinical trial, which, according to the definition in this text, must involve human beings, will have variability in adherence with the intervention and the study procedures. There are several reasons for low adherence. Life events such as illnesses, loss of employment, or divorce are factors associated with reduced adherence. In addition, participants may not perceive any treatment benefit, they may be unwilling to change their behaviors, they are forgetful, may lack family support, or ultimately they may change their minds regarding trial participation. Another reason for low adherence is adverse effects to the medication or intervention. Therefore, even studies of a one-time intervention such as surgery or a single medication dose can suffer from nonadherence. In fact, some surgical procedures can be declined or even be reversed. In addition, the participant's condition may deteriorate, and thus require termination of the study treatment or a switch from control to intervention. In a clinical trial in stable coronary disease, participants were randomized to percutaneous coronary intervention (PCI) plus optimal medical therapy compared to optimal medical therapy alone [12]. Among the 1,149 participants in the PCI group, 46 never underwent the procedure and another 27 had lesions that could not be opened. During a median follow-up of 4.6 years, 32.6% of the 1,138 participants in the optimal medical therapy alone group had revascularization. The trial showed no difference for the primary outcome of all-cause mortality or non-fatal myocardial infarction. However, it is difficult to determine how much the cross-overs influenced the overall finding. Moreover, such a trial can be considered to be testing the initial intervention strategy, with recognition that those who fail medical therapy will often have revascularization.

Most of the available information on adherence is obtained from the clinical therapeutic encounter rather than from the clinical trial setting. Although the differences between patients and volunteer clinical trial participants are important, and agreement to participate tends to minimize low adherence rates in trials, the basic principles observed in practice settings apply to research as well. In clinical trial databases, it has been shown that adherence to intervention, and even adherence to placebo, is independently associated with improved survival [13]. This observation suggests that adherent behavior may have benefits, or at least that adherence is associated with unmeasured factors related to better outcome. The results of a trial can be affected by low adherence to the intervention leading to an underestimation of possible therapeutic as well as potential toxic effects, and can undermine even a properly designed study. Data from a meta-analysis suggest that the difference in health benefits between high and low adherence has been shown to reach 26% [14]. Given the intention-to-treat principle of analysis (see Chap. 18), in order to maintain equivalent power, a 20% reduction in drug adherence may result in the need for a greater than

50% increase in sample size and 30% reduction will require doubling of the study cohort (see Chap. 8). Poor adherence is especially problematic in non-inferiority trials, where it will bias the results toward no difference between the intervention and control groups and decrease the reliability of the observed results.

Considerations Before Participant Enrollment

There are three major considerations affecting adherence to the study medications that investigators and sponsors ought to consider during the planning phase. First, efforts should be made to limit the impact of design features that may adversely influence the level of adherence. Second, steps should be taken to avoid enrollment of study participants who are likely to have low adherence while not being so restrictive as to decrease the generalizability of the results. Third, the research setting influences participant adherence over the long term. It is important to have realistic estimates of the adherence level during a trial, so that proper upward adjustments of the sample size can be made during the planning phase. Even practice-based trials that attempt to mimic real-life situations need to consider adherence in their designs.

Design Factors

Four study design factors can influence adherence—study duration, setting, simplicity of the regimen and the use of a run-in period.

Study duration influences adherence. The shorter the trial, the more likely participants are to adhere with the intervention regimen. A study in which intervention is started and completed in 1 day (such as fibrinolytic therapy for acute myocardial infarction or stroke) or during a hospital stay has great advantages over longer trials with regards to adherence. Trials in which the participants are under supervision, such as hospital-based ones, tend to have fewer problems with low adherence [15]. It is important to be mindful of the fact that there is a difference between special hospital wards and clinics with trained staff who are familiar with research requirements and general medical or surgical wards and clinics, where research experience might not be common or protocol requirements might not be appreciated. Regular hospital staff have many other duties which compete for their attention, and they perhaps have little understanding of the need for precisely following a study protocol and the importance of good adherence. On the other hand, if the intent is to assess how an intervention may perform in general practice, the regular clinical setting may have advantages.

The *setting* of the trial is also important. Whenever the study involves participants who will be living at home, the chances for low adherence increase. Studies of interventions that require changing a habit are particularly susceptible to this

hazard. A challenge is dietary studies. A participant may need special meals, which are different from those consumed by other family members. It may be difficult to adhere when having meals outside the home. Multiple educational sessions and preparation of meals by the investigator team may be necessary. Family involvement is essential, especially if the participant is not the usual meal preparer [16, 17]. In studies, when the participants' sources of food come only from the hospital kitchen or are supplied by the trial through a special commissary [18], participants are more likely to adhere with the study regimen than when they buy and cook their own food. This may also allow for blinded design.

The treatment regimen is an important factor and *simplicity* facilitates adherence. Single daily dose drug regimens are preferable to multiple daily dose regimens. Despite a simple regimen, 10–40% of participants have imperfect dosing [10]. A review of 76 trials, in which electronic monitors were used, showed that adherence is inversely proportional to the frequency of dosing [19]. Patients on a four-times-a-day regimen achieved on-schedule average adherence rates of about 50%. Adhering to multiple study interventions simultaneously poses special difficulties. For example, behavior changes such as quitting smoking, losing weight and reducing the intake of saturated fat at the same time requires highly motivated participants. Unlike on-going interventions such as drugs, diet, or exercise, trials of surgery and vaccination generally have the design advantage, with few exceptions, of enforcing adherence with the intervention.

Where feasible, a *run-in* period before actual randomization may be considered to identify those potential participants who are likely to become poor adherers and thereby exclude them from long-term trials. During the run-in, potential participants may be given either active medication or placebo over several weeks or months. An active run-in also allows identification of potential participants who do not have a favorable response to treatment on a biomarker or who develop side effects prior to randomization [20]. However, this design may be less informative about the effects of a treatment in practice, where the question for the clinician is whether or not to use it, not whether to use it after determining tolerability. A placebo run-in allows a determination of the potential participant's willingness to comply with the study intervention. Run-in phases were common already in 2001 when a literature search resulted in more than 1,100 examples of trials in which run-in phases were used [21]. This approach was successfully employed in a trial of aspirin and beta-carotene in US physicians [22]. By excluding physicians who reported taking less than 50% of the study pills, the investigators were able to randomize excellent adherers. After 5 years of follow-up, over 90% of those allocated to aspirin reported still taking the pills. An additional goal of the run-in is to stabilize the potential trial participants on specific treatment regimens or to wash-out the effects of discontinued medications. Though the number of participants eliminated by the run-in period is usually small (5–10%), it can be important as even this level of low adherence affects study power. A potential disadvantage of a run-in is that participants may notice a change in their medication following

randomization thereby influencing the blinding of the assignment. It also delays entry of participants into a trial, perhaps by a few weeks.

Berger et al. [21] raised the issue of external validity of the findings of trials that excluded potential poor adherers during a run-in phase. Can the results from trials with run-in selection of participants reasonably be fully extrapolated to all those patients meeting the trial eligibility criteria? The question about the generalizability of trial findings can be raised regarding the PARADIGM HF trial of patients with heart failure [23]. The trial had two consecutive run-in phases—the first over 2 weeks with enalapril and a second over 4 weeks with a valsartan-neprilysin inhibitor. A large number (20%) of eligible participants were excluded mostly due to adverse events (see Chap. 4). As always, whether to use a run-in depends on the question being posed. Does the trial have many exclusion criteria (a so-called efficacy trial) or few exclusions (a pragmatic or effectiveness trial)? Stated differently: What is the effect of the intervention in optimal circumstances? Or, what is the effect when, as is common in clinical settings, a large number of people fail to adhere to prescribed medication? Both are valid questions, but in the latter situation, as noted earlier, a larger sample size will be required. Lee et al. [24] compared the effect size in 43 clinical trials of selective serotonin uptake inhibitors in patients with depression that included a placebo run-in and those that did not. They found no statistically significant difference in the results.

In another approach, the investigator may instruct prospective participants to refrain from taking the active agent and then evaluate how well his request was followed. In the Aspirin Myocardial Infarction Study, for instance, urinary salicylates were monitored before enrollment, and very few participants were excluded because of a positive urine test.

Participant Factors

An important factor in preventing adherence problems is the *selection of appropriate participants*. Ideally, only those people likely to follow the study protocol should be enrolled. In the ACCORD trial, the screenees' willingness to test blood sugars frequently was taken as a measure of commitment to participate [25]. This may, however, influence the ability to generalize the findings (see Chap. 4 for a discussion of generalization). Several articles have reported that there is convincing evidence that nonadherers are substantially different from adherers in ways that are quite independent of the effects of the treatment prescribed [10, 26].

Exclusion of individuals who are unlikely to be good participants is usually advisable unless the trial is aimed at those individuals. A number of participant-related factors have been shown to negatively affect adherence [11]. People with *cognitive impairment* or *low literacy* are likely to have more problems with adherence [27]. It is obviously important that participants understand instructions

and follow through on these. A related issue is *low self-efficacy*, which relates to a person's ability to follow through with recommendations or make behavior change a permanent feature of his/her life [28]. It is important that participants believe in their own ability to do so. *Positive health beliefs* and attitudes (i.e., less fear of adverse effects) are also helpful. *Mental health issues* represent other predictors of poor adherence. Meta-analyses have shown that depressed patients have a 2 to 3-fold higher rate of nonadherence compared to those who were not depressed [26]. However, a successful behavioral weight-loss intervention in persons with serious mental illness was recently reported [29]. A combination of group and individual weight-management sessions and group exercise sessions over 18 months led to a statistically significant weight reduction in the intervention group compared to the control group. The connection with anxiety is less clear. A person's personality or characteristic traits may also be a factor to consider. *Conscientiousness* predicts good adherence and hostility poor adherence [26]. Similarly, those with a known history of missed appointments or adherence problems might be considered for exclusion. *Logistic factors* may also influence adherence, for example, persons who live too far away, or those who are likely to move before the scheduled termination of the trial. Traveling long distances may be an undue burden on disabled people. Those with *concomitant disease* may be less adherent because they have other medicines to take or are participating in other trials. Furthermore, it is important to be aware of the potential for contamination of the study results by these other medicines or trials. When applicable, the factors discussed above should be incorporated in the study exclusion criteria. These factors are difficult to define, so the final decision often is left to the discretion of the study investigator.

Financial and other incentives to motivate adherence are sometimes offered. These have been reported to improve adherence [30–32]. A concern is that financial incentives, if excessive, may lead to enrollment of participants more interested in the payment than in supporting science. As discussed in Chap. 2, Institutional Review Boards and others would view this practice as unethical.

An *informed participant* appears to be a better adherer. Proper education of the participant and the participant's family or caregiver is thought to be the most positive factor to high adherence, but the scientific evidence is not conclusive [33]. However, for ethical concerns, the participant (or, in special circumstances, his guardian) in any trial should be clearly instructed about the study and told what is expected from him. He should have proper insight into his illness and be given a full disclosure of the potential effects—good and bad—of the study medication. Sufficient time should be spent with a candidate and he should be encouraged to consult with his family or private physician. A brochure with information concerning the study is often helpful. As an example, the pamphlet used in the NIH-sponsored Women's Health Initiative trial is shown in Box 14.1. Many clinical trials develop websites with educational material directed at physicians and potential participants.

Box 14.1: Women's Health Initiative Brochure

What is the Women's Health Initiative?
The Women's Health Initiative (WHI) is a major research study of women and their health. It will help decide how diet, hormone therapy, and calcium and vitamin D might prevent heart disease, cancer, and bone fractures. This is the first such study to examine the health of a very large number of women over a long period of time. About 160,000 women of various racial and ethnic backgrounds from 45 communities across the United States will take part in the study.

Who can join the WHI?
You may be able to join if you are:

- a woman 50–79 years old
- past menopause or the "change of life"
- planning to live in the same area for at least 3 years

Why is this study important?
Few studies have focused on health concerns unique to women. Being a part of this important project will help you learn more about your own health. You will also help doctors develop better ways to treat all women. This study may help us learn how to prevent the major causes of death and poor health in women: heart disease, cancer, and bone fractures.

What will I be asked to do?
If you agree to join us, you will be scheduled for several study visits. These visits will include questions on your medical history and general health habits, a brief physical exam, and some blood tests. Based on your result, you may be able to join at least one of the following programs.

- **Dietary**: In this program you are asked to follow either your usual eating pattern or a low-fat eating program.
- **Hormone**: In this program you are asked to either take hormone pills or inactive pills (placebos). If you are on hormones now, you would need to talk with your doctor about joining this program.
- **Calcium and Vitamin D**: In this program you are asked to either take calcium and vitamin D or inactive pills. Only women in the Dietary or Hormone programs may join this program.
- **Health Tracking**: If you are not able to join the other programs, your medical history and health habits will be followed during the study.

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Box 14.1 (continued)

How long will the study last?
You will be in the study for a total of 8–12 years, depending on what year you enter the study. This period of time is necessary to study the long-term effects of the programs.

How will I benefit?
If you join the study, your health will be followed by the staff at our center. Certain routine tests will be provided, although these are not meant to replace your usual health care. Depending on which program you join, you may receive other health-care services, such as study pills and dietary sessions. You will not have to pay for any study visits, tests, or pills.

You will also have the personal satisfaction of knowing that results from the WHI may help improve your health and the health of women for generations to come.

Social support and involvement have emerged as major determinants of adherence [34]. Thus, it is recommended that family members, significant others or friends be informed about the trial and its expectations at the same time as the potential participant. After all, a large proportion of participants join trials at the support of family and friends [35]. The support they can offer in terms of assistance, encouragement and supervision can be very valuable. Practical support is most consistently associated with greater medication adherence [34]. Support is especially important in trials of lifestyle interventions. For example, cooking classes for spouses as well as participants have been very effective in dietary intervention trials [16, 17].

Major factors associated with low adherence are summarized in Table 14.1, listed in alphabetical order. Most of them are, as would be expected, the opposite of factors associated with high adherence. The consensus is that older persons generally show higher rates of adherence.

Table 14.1 Factors associated with low adherence

Cognitive impairments
Complexity of drug regimen
Concomitant diseases
Hostile personality
Lack of information and inadequate instructions
Lack of social support
Logistic factors
Low self-efficacy
Low literacy
Mental health issues, primarily depression
Negative health beliefs
Unsatisfying participant-investigator relationship

Adapted from Williams, Haskard-Zolnierik & DeMatteo [26]

Studies have shown that patients' recall of medical topics discussed with providers is poor and between 40–80% is forgotten immediately [36] while up to half of the information retained by patients is incorrect [37]. The "teach-back" method can be used to improve knowledge retention among patients [38] and confirm that patients understand what they have been told. If the investigator says to the study participant that he has high blood pressure that needs treatment, the participant would say, "I have high blood pressure that needs treatment." When told to take one pill every morning until the next clinic visit, the participant would repeat, "I should take one pill every morning until I return for my next clinic visit." When the participants accurately explain in their own words what they have been told their understanding is confirmed. A recent study of hospitalized patients with heart failure showed a trend toward lower readmissions for heart failure among those with more correct answers to teach-back questions [39].

Maintaining Good Participant Adherence

The foundation for high adherence during a trial is a well-functioning setting with committed clinic staff (Table 14.2). Establishing a positive research setting at the first contact with future participants is a worthwhile investment for the simple reason that satisfied participants are better adherers. A warm and friendly relationship between participants and staff established during the recruitment phase should be nurtured. This approach covers the spectrum from trusting interactions, adequate time to discuss complaints, demonstrating sincere concern and empathy, when appropriate, convenient clinic environment, short waiting times, etc. "Bonding" between the participant and clinical trials staff members is a recognized and powerful force in maintaining good adherence. The clinic visits should be pleasant and participants should be encouraged to contact staff between scheduled visits if they have questions or concern. Close personal contact is key. Clinic staff may employ various means of engagement, including phone calls, mail and e-mail. Sending cards

Table 14.2 Factors in improving likelihood of medication adherence in clinical trials

Approach	Activity
Trial design	Simple schedule (once or twice daily dosing) that fits into daily routine [40]
Relationships and communication	Enhanced relationship of study coordinator with participant with regular communication [41, 42]
Passive monitoring	Electronic monitoring tools
Education	Medication usage skills [33]
Reinforce beliefs	Association activities using medication-outcome relationships
Reminders	Alarms (e.g., set watch or cell phone reminders to medication schedule) and associations (e.g., put medication beside toothbrush or use a behavior trigger)
Incentives	Monetary or other rewards

on special occasions such as birthdays and holidays is a helpful gesture. Visiting the participant if he is hospitalized demonstrates concern. It is helpful to investigators and staff to make notes of what participants tell them about their families, hobbies and work so that in subsequent visits they can follow-up and show interest and involvement. Other valued factors are free parking and, for working participants, opportunities for evening or weekend visits. For participants with difficulties attending clinic visits, home visits by staff could be attempted. Continuity of care is ranked as a high priority by participants. Continued family involvement is especially important during the follow-up phase.

During a study, it is important to keep the participants informed about relevant published findings from related trials. They should also be reminded, when applicable, that a data monitoring committee is reviewing the trial data for safety and efficacy throughout the duration of the trial which should be described to them. Brief communications from this committee assuring the participants that no safety concerns have been noted, can also be helpful.

The use of various types of general reminders can also reduce the risk of low adherence. Clinic staff should typically *remind* the participant of upcoming clinic visits or study procedures. Sending out postcards, calling, e-mailing or text messaging a few days before a scheduled visit can help. Paper-based reminders seem to be most effective [43]. A telephone call though has the obvious advantage that immediate feedback is obtained and a visit can be rescheduled if necessary—a process that reduces the number of participants who fail to keep appointments. Telephoning also helps to identify a participant who is ambivalent regarding his continued participation or who has suffered a study event. To preclude the clinic staff's imposing on a participant, it helps to ask in advance if the participant objects to being called frequently. Asking a participant about the best time to contact him is usually appreciated. Reminders can then be adjusted to his particular situation. In cases where participants are reluctant to come to clinics, more than one staff person might contact the participant. For example, the physician investigator could have more influence with the participant than the staff member who usually schedules visits. In summary, the quantity and quality of interaction between an investigator and the participant can positively influence adherence.

For drug studies, special *pill organizers* help the participant keep track of when to take the medication. These organizers allow participants to divide, by day and time of day, all medications prescribed during a 7-day period. If the participant cannot remember whether he took the morning dose, he can easily find out by checking the compartment of the pill box for that day. Special reminders such as noticeable stickers in the bathroom or on the refrigerator door or on watches have been used. Placing the pill bottles (child proof as appropriate) on the kitchen table or nightstand with the tooth brushes are other suggestions for participants.

The effectiveness of electronic reminders to improve medication and visit adherence in clinical trials has received much attention recently [43–45]. The rationale for their use is that one of the most commonly reported reasons for not being adherent is forgetfulness. Additionally, these simple interventions are less expensive and time-consuming than personal attention by investigators.

Vervloet et al. [46] conducted a comprehensive literature review and identified 13 studies meeting their inclusion criteria. Three types of automatic electronic reminders were considered—1) short reminder messages sent to the participant's mobile phone, 2) audiovisual reminders were sent through a specific electronic reminder device at predetermined times, and 3) text messages sent to a participant's pager to alert them to take the study medication. The main conditions studied were HIV, glaucoma, hypertension, and asthma. The review showed evidence for short-term (<6 months) effectiveness in 8 of the 13 studies, especially those of short messages sent through mobile phones. The effectiveness beyond 6 months was noted in only one of those studies. A potential weakness of these studies was that reminders were sent to all participants regardless of whether they took their study medication. This could have a negative impact. One of the studies reported that weekly reminders were more effective than daily reminders. Tailored messages may be more effective than standard text. This evolving technology has also been evaluated in clinical practice with mixed results [47].

Interventions to maintain good adherence for lifestyle changes can be very challenging. Most people have good intentions that can wane with time unless there is reinforcement. A special brochure, which contains essential information and reminders, may be helpful in maintaining good participant adherence (Box 14.2). The telephone number where the investigator or staff can be reached should be included in the brochure.

Box 14.2: Aspirin Myocardial Infarction Study Brochure

Text of brochure used to promote participant adherence in the Aspirin Myocardial Infarction Study. DHEW Publication No. (NIH) 76-1080.

1. **Your Participation in the Aspirin Myocardial Infarction Study (AMIS) is Appreciated**! AMIS, a collaborative study supported by the National Heart and Lung Institute, is being undertaken at 30 clinics throughout the United States and involves over 4,000 volunteers. As you know, this study is trying to determine whether aspirin will decrease the risk of recurrent heart attacks. It is hoped that you will personally benefit from your participation in the study and that many other people with coronary heart disease may also greatly benefit from your contribution.
2. **Your Full Cooperation is Very Important to the Study**. We hope that you will follow all clinic recommendations contained in this brochure, so that working together, we may obtain the most accurate results. If anything is not clear, please ask your AMIS Clinic Physician or Coordinator to clarify it for you. *Do not hesitate to ask questions*.
3. **Keep Appointments**. The periodic follow-up examinations are very important. If you are not able to keep a scheduled appointment, call the

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Box 14.2 (continued)

Clinic Coordinator as soon as possible and make a new appointment. It is also important that the dietary instructions you have received be followed carefully on the day the blood samples are drawn. At the annual visit, you must be *fasting*. At the non-annual visits you are allowed to have a *fat-free diet*. Follow the directions on your Dietary Instruction Sheet. *Don't forget to take your study medication as usual on the day of your visit*.

4. **Change in Residence**. If you are moving within the Clinic area, please let the Clinic Coordinator know of your change of address and telephone number as soon as possible. If you are moving away from the Clinic area, every effort will be made to arrange for continued follow-up here or at another participating AMIS clinic.
5. **Long Vacations**. If you are planning to leave your Clinic area for an extended period of time, let the Clinic Coordinator know so that you can be provided with sufficient study medication. Also give the Clinic Coordinator your address and telephone number so that you can be reached if necessary.
6. **New Drugs**. During your participation in AMIS you have agreed not to use non-study prescribed aspirin or aspirin-containing drugs. Therefore, please call the Clinic Coordinator before starting any new drug as it might interfere with study results. At least 400 drugs contain aspirin, among them cold and cough medicines, pain relievers, ointments and salves, as well as many prescribed drugs. Many of these medications may not be labeled as to whether or not they contain aspirin or aspirin-related components. To be sure, give the Clinic Coordinator a call.
7. **Aspirin-Free Medication**. Your Clinic will give you aspirin-free medication for headaches, other pains and fever at no cost. The following two types may be provided.
   - Acetaminophen. The effects of this drug on headaches, pain and fever resemble those of aspirin. The recommended dose is 1–2 tablets every 6 h as needed or as recommended by your Clinic Physician.
   - Propoxyphene hydrochloride. The drug has an aspirin-like effect on pain only and cannot be used for the control of fever. The recommended dose is 1–2 capsules every 6 h as needed or as recommended by your Clinic Physician.
8. **Study Medication**. You will be receiving study medication from your Clinic. You are to take two capsules each day unless prescribed otherwise. Should you forget to take your morning capsule, take it later during the day. Should you forget the evening dose, you can take it at bedtime

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Box 14.2 (continued)

with a glass of water or milk. The general rule is: *Do not take more than 2 capsules a day*.

9. **Under Certain Circumstances It Will Be Necessary to Stop Taking the Study Medication**:
   - If you are hospitalized, stop taking the medication for the period of time you are in the hospital. Let the Clinic Coordinator know. After you leave the hospital, a schedule will be established for resuming medication, if it is appropriate to do so.
   - If you are scheduled for surgery, we recommend that you stop taking your study medication 7 days prior to the day of the operation. This is because aspirin may, on rare occasions, lead to increased bleeding during surgery. In case you learn of the plans for surgery less than 7 days before it is scheduled, we recommend that you stop the study medication as soon as possible. And again, please let the Clinic Coordinator know. After you leave the hospital, a schedule will be established for resuming medication, if it is appropriate to do so.
   - If you are prescribed non-study aspirin or drugs containing aspirin by your private physician, stop taking the study medication. Study medication will be resumed when these drugs are discontinued. Let the Clinic Coordinator know.
   - If you are prescribed anti-coagulants (blood thinners), discontinue study medication and let your Clinic Coordinator know.
   - If you have any adverse side effects which you think might be due to the study medication, stop taking it and call the Clinic Coordinator immediately.
10. **Study-Related Problems or Questions**. Should you, your spouse, or anyone in your family have any questions about your participation in AMIS, your Clinic will be happy to answer them. The clinic would like for you or anyone in your family to call if you have any side effects that you suspect are caused by your study medication and also if there is any change in your medical status, for example, should you be hospitalized.
11. **Your Clinic Phone Number Is on the Back of This Brochure. Please Keep This Brochure as a Reference Until the End of the Study**.

A commonly asked question is whether a low adherence rate should be discussed directly with study participants. There is a consensus that any discussion should not be confrontational. The preferred approach is to open any discussion by saying that adherence to medications can be very difficult for many people. After being given examples of common reasons for low adherence, many participants seem to be more willing to discuss their own situations and adherence problems. Thus,

sympathy and understanding may be helpful if followed by specific recommendations regarding ways to improve adherence. A large number of interviewing techniques of patients in the clinical setting are discussed by Shea [48]. Tools like the Morisky Scale [49] could be used to identify participants at high risk for non-adherence on whom to focus preventive efforts.

A remarkable recovery program was developed and implemented by Probstfield et al. [50]. Through participant counseling, the investigators succeeded in about 90% of the 36 drop-outs in approximately 6 months to return for clinic visits. Even more notable was the virtual absence of recidivism over the remaining 5 years of intervention. Approximately 70% of the drop-outs resumed taking their study medication, though typically at a lower dose than specified in the protocol.

Adherence Monitoring

Monitoring adherence is important in a clinical trial for two reasons: first, to identify any problems so steps can be taken to enchance adherence; second, to be able to relate the trial findings to the level of adherence. In general, analysis of trial outcomes by level of adherence is strongly discouraged as it can in fact lead to serious bias, the direction of which cannot always be predicted (see Chap. 18). However, in so far as the control group is not truly a control and the intervention group is not being treated as intended, group differences are diluted, and generally lead to an underestimate of both the therapeutic benefit and the adverse effects. Differential adherence to two equally effective regimens can also lead to possibly erroneous conclusions about the effects of the intervention. The level of adherence that occurred can also be compared with what was expected when the trial was designed.

In some studies, measuring adherence is relatively easy. This is true for trials in which one group receives surgery and the other group does not, or for trials which require only a one-time intervention such as a vaccine. Most of the time, however, assessment of adherence is more complex. No single measure of adherence gives a complete picture, and all are subject to possible inaccuracies and varying interpretations. Furthermore, there is no widely accepted definition or criterion for either high or low adherence. A review of 192 publications showed that only 36% assessed and adequately reported medication adherence [51]. The level of adherence that occurred can also be compared to what was expected when the trial was designed.

In monitoring adherence for a long-term trial, the investigator may also be interested in changes over time. When reductions in adherence are noted, corrective action can possibly be taken. This monitoring could be by calendar time (e.g., current 6 months versus previous 6 months) or by clinic visit (e.g., follow-up visit number four versus previous visits). In multicenter trials, adherence to the intervention also ought to be examined by clinic or by region in multinational trials. In all studies, it is important for clinic staff to receive feedback about level of adherence. In double-blind trials where data by study group generally should not be disclosed, the adherence data can be combined for the study groups. In trials that

are not double-blind, all adherence tables can be reviewed with the clinic staff. Frequent determinations obviously have more value than infrequent ones. A better indication of true adherence can be obtained. Moreover, when the participant is aware that he is being monitored, frequent measures may encourage adherence.

There are several indirect methods of assessing adherence. In drug trials, *pill or capsule count*, is the easiest and most commonly used way of evaluating participant adherence. Since this assumes that the participant has ingested all medication not returned to the clinic, the validity of pill count is debated. For example, if the participant returns the appropriate number of leftover pills at a follow-up visit, did he in fact take what he was supposed to, or take only some and throw the rest out? Pill count is possible only as long as the pills are available to be counted. Participants sometimes forget or neglect to bring their pills to the clinic to be counted. In such circumstances, the investigator may ask the participant to count the pills himself at home and to notify the investigator of the result by telephone. Obviously, these data may be less reliable. The frequency with which data on pill counts are missing gives an estimate of the reliability of pill count as an adherence measure.

In monitoring pill count, the investigators ought to anticipate questions of interest to readers of the trial report when published. What was the overall adherence to the protocol prescription? If the overall adherence with the intervention was reduced, what was the main reason for the reduction? Were the participants prescribed a reduced dose of the study medication, or did they not follow the investigator's prescription? Were there differences between the study groups with regard to protocol dosages, investigator prescriptions, or participant adherence to the prescribed dosages? What were the reasons for reduced participant adherence? Was it because of intervening life events, specific adverse effects or was it simply forgetfulness? The answers to these questions may increase the understanding and interpretation of the results of the trial.

When discussing adherence assessed by pill count, the investigator has to keep in mind that these data may be inflated and misleading. Additionally, these data do not include information from participants who omit a visit. Most participants tend to overestimate their adherence either in an effort to please the investigator or because of faulty memory. Those who miss one or more visits typically have low adherence. Therefore, the adherence data should be viewed within the framework of all participants who are scheduled to be seen at a particular visit. There is general agreement on one point—the participant who says he did not take his study medication can be trusted.

Electronic monitoring of adherence has been used [52, 53]. A device electronically records drug package opening times and duration, thus, describes dosing histories. The correlation between package openings and measured drug concentrations in serum is very high. The obvious advantage of electronic monitoring is that the dose-timing can be assessed to see if it is punctual and regular. In an HIV trial, overall adherence was 95%, but only 81% of the doses were taken within the prescribed dosing interval (±3 h) [52]. In a study of hypertensive participants, about 10% of the scheduled doses were omitted on any day [53]. Drug holidays, defined as omissions of all doses during 3 or more days, were recorded in 43% of

the participants. An interesting observation was that participants with dosing problems were more likely later to become permanent drop-outs. It is not known whether or to what extent low adherence to dose-timing influences the trial findings.

A recent development is an FDA-approved device which has a body-worn sensor or patch that collects physiological and behavioral metrics generated by an ingestible sensor. The system can be used to monitor when the patient takes his medication. This sensor is embedded inside an inactive tablet and it activates and communicates its presence and unique identifier to the patch [54].

Indirect information on adherence can also be obtained through *interviews or record keeping* by the participant. A diet study might use a 24-h recall or a 7-day food record. Exercise studies may use diaries to record frequency and kind of exercise. Trials of people with angina might record frequency of attacks or pain and nitroglycerin consumption.

There are two major direct methods for measuring adherence. *Biochemical analyses* are sometimes made on either blood or urine in order to detect the presence of the active drug or metabolites. A limitation in measuring substances in urine or blood is the short half-life of most drugs. Therefore, laboratory determinations usually indicate only what has happened in the preceding day or two. A control participant who takes the active drug (obtained from a source outside the trial) until the day prior to a clinic visit, or a participant in the intervention group who takes the active drug only on the day of the visit might not always be detected as being a poor adherer. Moreover, drug adherence in participants taking an inert placebo tablet cannot be assessed by any laboratory determination. Adding a specific chemical substance such as riboflavin can serve as a marker in cases where the placebo, the drug or its metabolites are difficult to measure. However, the same drawbacks apply to markers as to masking substances—the risk of toxicity in long-term use may outweigh benefits.

Laboratory tests obtained on occasions not associated with clinic visits may give a better picture of regular or true adherence. Thus, the participant may be instructed, at certain intervals, to send a vial of urine to the clinic. Such a technique is of value only so long as the participant does not associate this request with an adherence monitoring procedure. In at least one study, information obtained in this manner contributed no additional information to laboratory results done at scheduled visits, except perhaps as a confirmation of such results.

Measurement of *physiological response variables* can be helpful in assessing adherence. Cholesterol reduction by drug or diet is unlikely to occur in 1 or 2 days. Therefore, a participant in the intervention group cannot suddenly adhere with the regimen the day before a clinic visit and expect to go undetected. Similarly, the serum cholesterol level of a nonadherent control participant is unlikely to rise in the 1 day before a visit if he skips the non-study lipid-lowering drug. Other physiological response variables that might be monitored are blood pressure in an antihypertensive study, carbon monoxide in a smoking study, platelet aggregation in an aspirin study, and graded exercise in an exercise study. In all these cases, the indicated response variable would not be the primary response variable but merely an intermediate indicator of adherence to the intervention regimen. Unfortunately,

not every person responds in the same way to medication, and some measures, such as triglyceride levels, are highly variable. Therefore, indications of low adherence of individual participants using these measures are not easily interpreted. Group data, however, may be useful.

Another aspect of monitoring deals with participant adherence to study procedures such as attendance at scheduled visits or *visit adherence*. One of the major purposes of these visits is to collect response variable data. The data will be better if they are more complete. Thus, completeness of data in itself can be a measure of the quality of a clinical trial. Studies with even a moderate amount of missing data or participants lost to follow-up could give misleading results and should be interpreted with caution. By reviewing the reasons why participants missed scheduled clinic visits, the investigator can identify factors that can be corrected or improved. Having the participants come in for study visits facilitates and encourages adherence to study medication. Study drugs are dispensed at these visits and the dose is adjusted when necessary.

From a statistical viewpoint, every randomized participant should be included in the primary analysis (Chaps. 8 and 18). Consequently, the investigator must keep trying to get all participants back for scheduled visits until the trial is over. Even if a participant is taken off the study medication by an investigator or stops taking it, he should be encouraged to come in for regular study visits or at least be followed by telephone. Complete follow-up data on the response variables are critical so visit adherence is important. In addition, participants do change their minds. For a long time, they may want to have nothing to do with the trial and later may agree to come back for visits and even resume taking their assigned intervention regimen. Special attention to the specific problems of each participant withdrawn from the trial and an emphasis on potential contribution to the trial can lead to successful retrieval of a large proportion of withdrawn participants. Inasmuch as the participant will be counted in the analysis, leaving open the option for the participant to return to active participation in the study or at least agree to a visit or phone contact at the end of the trial is worthwhile.

The purpose of adherence monitoring is to acquire a general understanding of the level of adherence, so steps can be taken to improve it if necessary. Thus, there is limited value in obtaining precise assessments since we don't favor data analysis by adherence.

Dealing with Low Adherence

If low adherence is related to difficulties making appointments, it may be useful to offer more convenient clinic hours, such as evenings and weekends as mentioned above. Home visits are another option for participants with disabilities who have difficulties making it to the clinic. For participants who have moved, the investigator might be able to arrange for follow-up in other cities.

One of the challenges in clinical trials is the complete ascertainment of response variables in participants who are no longer actively involved in the trial. The

Internet provides opportunities to track participants lost to follow-up. There are both fee-for-service and free search engines. The basic information required for a search is complete name, birth date and Social Security Number or some other specific identification number. These searches are more effective if several and if different search engines are employed.

Steps should be taken to prevent situations in which participants request that they never be contacted. These are sometimes referred to as complete withdrawal. Participants who end their active participation in a clinical trial often agree to be contacted at the end of the trial for ascertainment of key response variables. For those who are lost to follow-up, but have not withdrawn their consent, alternative sources of information are family members and medical providers. The goal is to limit the amount of missing information.

Special Populations

Although the approaches to dealing with prevention of low adherence and maintenance of high adherence are generally applicable, there are factors that need consideration when dealing with special populations. Older adults represent a growing number of participants in clinical trials. They typically have more health complaints than their younger counterparts. There is a rich literature on factors that may influence adherence and on strategies to increase adherence in the clinical setting among older people. Many of these are highly relevant for clinical trials.

There are special challenges of maintaining adherence in patients with chronic health illnesses. Specific management interventions for several prevalent conditions are highlighted in the Handbook of Health Behavior Change [11]. These include cardiovascular diseases [55], diabetes [56], chronic respiratory diseases [57], chronic infectious diseases [58], cancer [59] and obesity [60].

References

1. Haynes RB, Taylor DW, Sackett DL (eds.). *Compliance in Health Care*. Baltimore: Johns Hopkins University Press, 1979.
2. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health* 2008;11:44-47.
3. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691-705.
4. Zeber JE, Manias E, Williams AF, et al. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR medication adherence & persistence special interest group. *Value Health* 2013;16:891-900.
5. Raebel MA, Schmittdiel J, Karter AJ, et al. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51:S11-S21.

6. Eapen Z, Mi X, Qualls LG, et al. Adherence and persistence in the use of warfarin after hospital discharge among patients with heart failure and atrial fibrillation. *J Card Fail* 2014;20:23-30.
7. Granger BB, Rusincovitch SA, Avery S, et al. Missing signposts on the roadmap to quality: a call to improve medication adherence indicators in data collection for population research. *Front Pharmacol* 2013;4:139.
8. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health-Syst Pharm* 2003;60:657-665.
9. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. *N Engl J Med* 2010;362:1553-1555.
10. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-497.
11. Riekert KA, Ockene JK, Pbert L (eds.). *The Handbook of Health Behavior Change* (4th edition). New York: Springer Publishing Company, 2014.
12. Boden WE, O'Rourke RA, Teo KK, et al for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-1516.
13. Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomized, controlled clinical trial. *Lancet* 2005;366:2005-2011.
14. DiMatteo MR. Variations in patients' adherence to medical recommendations. A quantitative review of 50 years of research. *Med Care* 2004;42:200-209.
15. Härkäpää K, Järvikoski A, Mellin G, Hurri H. A controlled study of the outcome of inpatient and outpatient treatment of low back pain. Part I. Pain, disability, compliance, and reported treatment benefits three months after treatment. *Scand J Rehabil Med* 1989;21:81-89.
16. McLean N, Griffin S, Toney K, Hardeman W. Family involvement in weight control, weight maintenance and weight-loss interventions: a systematic review of randomised trials. *Intern J Obesity* 2003;27:987-1005.
17. Voils CI, Yancy Jr WS, Kovac S, et al. Study protocol: Couples Partnering for Lipid Enhancing Strategies (CouPLES)—a randomized, controlled trial. *Trials* 2009;10:10-19.
18. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;344:3-10.
19. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23:1296-1310.
20. Probstfield JL. The clinical trial prerandomization compliance (adherence) screen. In Cramer JA, Spilker B (eds.). *Patient Compliance in Medical Practice and Clinical Trials.* New York: Raven Press, 1991.
21. Berger VW, Rezvani A, Makarewicz VA. Direct effect on validity of response run-in selection in clinical trials. *Control Clin Trials* 2003;24;156-166.
22. Lang JM, Buring JE, Rosner B, et al. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med* 1991;10:1585-1593.
23. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
24. Lee S, Walker JR, Jakul L, Sexton K. Does elimination of placebo responders in a placebo run-in increase the treatment effect in randomized clinical trials? A meta-analytic evaluation. *Depress Anxiety* 2004;19:10-19.
25. Kingry C, Bastien A, Booth G, et al. for the ACCORD Study Group. Recruitment strategies in the Action to Control Cardiovascular Risk of Diabetes (ACCORD) Trial. *Am J Cardiol* 2007;99[suppl]:68i-79i.
26. Williams SL, Haskard-Zolnierik KB, DiMatteo MR. Psychosocial predictors of behavioral change. In Riekert KA, Ockene JK, Pbert L (eds.). *The Handbook of Health Behavior Change* (4th edition). New York: Springer Publishing Company, 2014, pp. 69-86.

27. Youmans SL, Schillinger D. Functional health literacy and medication use: the pharmacist's role. *Ann Pharmacother* 2003;37:1726-1729.
28. Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Pat Educ Counsel* 2007;65:253-260.
29. Daumit GL, Dickerson FB, Wang NY, et al. A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med* 2013;368:1594-1602.
30. Kimmel SE, Troxel AB, Loewenstein G, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. *Am Heart J* 2012;164:268-274.
31. Ryan R, Santesso N, Lowe D. et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev* 2014;4: CD007768.
32. DeFulio A, Silverman K. The use of incentives to reinforce medication adherence. *Prev Med* 2012;55:S86-S94.
33. Hiligsmann M, Salas M, Hughes DA, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR medication adherence & persistence special interest group. *Osteoporos Int* 2013;24:2907-2918.
34. Scheurer D, Choudhry N, Swanton KA, et al. Association between different types of social support and medication adherence. *Am J Manag Care* 2012;18:e461-e467.
35. Barnes K. Patients provide insight into trial participation. Outsourcing-Pharma.com, July 4, 2007. www.outsourcing-pharma.com/content/view/print/135930.
36. Kessels RPC. Patients' memory for medical information. *J R Soc Med* 2003;96:219-222.
37. Anderson JL, Dodman S, Kopelman M, et al. Patient information recall in a rheumatology clinic. *Rheumatology* 1979;18:18-22.
38. Tamur-Lis W. Teach-back for quality education and patient safety. *Urol Nurs* 2013;33:267-271.
39. White M, Garbez R, Carroll M, et al. Is "teach-back" associated with knowledge retention and hospital readmission in hospitalized heart failure patients? *J Cardiovasc Nurs* 2013;28:137-146.
40. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin* 2014;29:1-8.
41. Demonceau J, Ruppar T, Kristanto P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013;73:545-562.
42. Zullig LL, Peterson ED, Bosworth HB. Ingredients of successful interventions to improve medication adherence. *JAMA* 2013;310:2611-2612.
43. Dexheimer JW, Sanders DL, Rosenbloom ST, et al. Prompting clinicians: A systematic review of prevention care reminders. *AMIA Annu Symp Proc. 2005;* 2005;938.
44. Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: a systematic review. *J Telemed Telecare* 2011;17:358-364.
45. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, et al. Mobile phone messaging reminders for attendance at healthcare appointments. *Cochrane Database of Systematic Reviews* 2013, Issue 12
46. Vervloet M, Linn AJ, vanWeert, JCM, et al. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *J Am Med Inform Assoc,* 2012; 19:696-704.
47. Granger BB, Bosworth H. Medication adherence: emerging use of technology. *Curr Opin Cardiol*. 2011; 26:279-287.
48. Shea SC. *Improving medication adherence: How to talk with patients about their medications*. Philadelphia: Lippincott, Williams & Wilkins, 2006.
49. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* 2008;10:348-354.

50. Probstfield JL, Russell ML, Henske JC, et al. Successful program for recovery of dropouts to a clinical trial. *Am J Med* 1986;80:777-784.
51. Gossec L, Tubach F, Dougados M, Ravaud P. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: A systematic literature review. *Am J Med Sci* 2007;334:248-254.
52. Vrijens B, Rousset E, Rode R, et al. Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models. *J Clin Pharmacol* 2005;45:461-467.
53. Vrijens B, Vincze G, Kristanto P, et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *Br Med J* 2008;336:1114-1117.
54. Proteus Digital Health, Inc. www.proteusdigitalhealth.com/technology/proteus-publications/
55. Hayman LL, Mruk MM. Chronic disease management interventions: cardiovascular disease. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 273-289.
56. Hood KK, Raymond JK, Harris MA. Diabetes management behaviors: The key to optimal health and quality of life outcomes. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 291-308.
57. Welkom JS, Riekert KA, Eakin, MN, et al. Behavioral management of chronic respiratory diseases: examples from asthma and chronic obstructive pulmonary disease. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 309-329.
58. Rhodes SD, Wilkin AM, Abraham C, Bachmann LH. Chronic infectious disease management interventions. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 331-345.
59. Peterman AH, Victorson D, Cella D. Adherence to treatment and lifestyle changes among people with cancer. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 347-362.
60. Burke LE, Turk MW. Obesity. In Riekert KA, Ockene JK, Pbert L (eds). *The Handbook of Health Behavior Change* (4th edition). New York, Springer Publishing Company, 2014, pp 363-378.