Adherence to Oral Anti-tumour Therapies

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Adherence to Oral Anti-tumour Therapies
Foreword

Non-adherence to oral anti-tumour therapies hid for many years behind the assumption that patients take their medication as prescribed. Only in recent years have professionals begun to reflect this in their practice, learned from experience with other serious chronic diseases, and considered the challenge of their patients facing the prospect of taking an oral drug for a long period of time.

The European Group for Blood and Marrow Transplantation (EBMT) Swiss Nurses Working Group realised early in 2010 that there is a lack of comprehensive, easily accessible literature to learn about adherence/non-adherence and possible ways to intervene. You are holding the first collaborative work of Erik Aerts, Sabine Degen Kellerhals and Monica Fiedner in your hands. We realise that the situation in other countries might be different to the Swiss situation but nevertheless we hope that this booklet is the start of an open communication between professionals and patients trying to understand the challenges of daily oral drug intake and having to deal with the potential side effects.

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1 Introduction to adherence / non-adherence

Adherence is acting in accordance with recommendations made by healthcare professionals, to which the patient has agreed after receiving detailed information. Nonadherence in patients with a chronic disease (e.g., patients with neoplasia), has been a recognised problem for a long time, not only with medical therapy but also with supportive therapies. Adherence thus includes the learning of self-care skills by a patient and hence supports the independence of a chronically ill person. If a patient does not adhere to the regimen, it can lead to serious consequences, such as relapse or other complications that ultimately have an impact on healthcare costs. An example of clinically relevant non-adherence was demonstrated in an isolation ward for patients with a haematological disease whose behaviour was inconsistent with the agreed hygienic guidelines (Hoodin, 1993). Whether this had consequences in terms of their treatment outcomes, however, remained unclear – the question was rather how many hygienic measures would be necessary to achieve the desired therapeutic result, which in turn had to be defined accordingly.

According to a report by the WHO (2003), on average only 50% of chronically ill patients undergoing long-term treatment are adherent. It has long been assumed that adherence was higher in cancer patients than in other groups of patients with a chronic disease, because it was assumed that patients diagnosed with cancer basically adhere to their therapy out of fear of unwanted side effects, recurrence or death. However, numerous studies show that there is never a 100% adherence in this population (e.g., Macintosh, Pond, Leung & Siu, 2007; Marin et al, 2010; Nilsson et al, 2006; Noens et al, 2009; Partridge et al, 2010).

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1 This refers to both female and male patients. The descriptions of patients in each following instance also relate to both women and men.
The consequences of non-adherence may be severe, so that the encouragement of adherence is an important task for all stakeholders so as to achieve and maintain the desired therapeutic result. This supports the reliable treatment of the patient, so that the can deal with his illness independently for a longer time. Adherence is a dynamic process in which different factors can contribute to whether a patient does or does not adhere to agreements (see Chapter 3 – Clinical consequences of non-adherence). It is important that adherent behaviour be repeatedly discussed in meetings with the patient and his family, and not taken for granted (see Chapter 5 – Patient / family education).

1.1 Definition of terms

What lies behind the word adherence, which is used variously in the literature? In 1979, Haynes and colleagues defined adherence (then still called “patient compliance”) as “the extent to which the behaviour of a patient – with regard to taking medication, following a diet and/or the execution of behavioural changes in lifestyle – is consistent with the recommendations of a specialist” (Haynes, Taylor & Sackett, 1979). This resulted in the term “cooperative behaviour” to describe the interaction of two or more persons or organisations pursuing a joint objective. The term “patient compliance” was introduced in 1975 and used until 2008. In 2009 the term “medication adherence” appeared in the Database of Terms of PubMed (http://www.ncbi.nlm.nih.gov). Medication adherence describes voluntary cooperation of the patient in taking medications as prescribed. The definition includes choosing the right time, the right dosage and the right frequency of ingestion by the patient. This describes not only complying with the agreed treatment, but also the prescribed dosage that must not be decreased (hypo-adherence) or increased (hyper-adherence) by the patient. Thus the role of the patient is understood not only as that of a passive recipient of recommendations, but as someone actively in-
volved in the treatment process. In the term database of PubMed the following keywords are listed under the term medication adherence: Adherence, Medication; Medication Compliance; Compliance, Medication; Medication Nonadherence; Nonadherence, Medication; Medication Non-Compliance; Medication Noncompliance; Noncompliance, Medication; Medication Non-Adherence; Medication Non Adherence; Non-Adherence, Medication; Medication Persistence; Persistence, Medication. In the English-speaking world there is mostly mention of “Adherence, Compliance, Persistence, Concordance or Medication Interest” (Hohneker, Shah–Mehta & Brandt, 2011), whereas in German-speaking areas the term is used primarily in other areas, such as HIV or diabetes – but seldom in oncology.

The understanding of the term adherence has changed in recent years as well. Whereas in the past it was still assumed that behind non-compliance is a failure on the part of the patient, today one more likely speaks of a failure of the health system that has not recognised the needs of patients and responded to them. Therefore, we now know that a patient who behaves non-adherently should be supported by all parties involved in his care and should not be blamed.

The term persistence describes the continuum from the start of treatment until the time at which the therapy is stopped. For example it was shown in a study that persistence dramatically decreases after the first 6 months of therapy (Tsang, Rudychev & Pescatore, 2006).
1.2 Incidence / Prevalence

The body of knowledge on the prevalence\(^2\) of non-adherence with regard to oral medication-treated tumours is small, since to date only a few controlled studies in this area have been conducted with sufficient explanatory power. One of the first studies that examined the medication adherence of tumour patients was published in 1983 (Hoagland, Morrow, Bennett & Carriere, 1983). Since then some studies have also investigated the adherence of patients with a tumour in combination with the prophylactic/therapeutic administration of antibiotics (Adachi et al, 2010) or adherence in patients with breast cancer, taking oral agents (e.g., Hershman et al, 2010; Lebovits et al, 1990; Mayer et al, 2009; McCowan et al, 2008; Moore, 2010, Partridge et al, 2010).

The prevalence of non-adherence in patients with chronic myeloid leukaemia (CML) varies considerably, depending on the studies conducted. For example, Noens and colleagues (2009) observed in a study a rate of perfect adherence of 14.2%. They also noted that some patients were even hyper-adherent, taking a higher dose than was prescribed by the doctor. Marin and colleagues (2010) found in a comparable population a mean adherence rate of 98% (variation range of 24%-104%). One consequence of poor adherence can be that the patient no longer responds adequately to treatment (for example, shows no adequate molecular response) (Ibrahim et al, 2011; Marin et al, 2010).

However, little is known about adherence with the use of oral anti-cancer drugs associated with gastrointestinal stromal tumours (GIST) and other rare tumours. There are more and more projects or surveys, however (e.g., www.conticanet.eu), that try to make this challenge visible, and also provide support for people affected.

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\(^2\) Prevalence describes the number of people who are sick at the time of an investigation; incidence refers to the number of new cases during a certain period of time.
1.3 Correlations / Predictors

What factors contribute to a patient complying with the treatment discussed or indeed having a difficulty doing so? The WHO (2003) assumes that adherence is a changeable process subject to time variations in disease progression. Usually circumstances in a patient’s life result in his being unable to comply with therapy in the way that has been agreed upon.

In this regard the WHO has identified five factors that can exert an influence on a patient’s adherence: factors of the health system, socioeconomic factors, factors of the disease, treatment factors and factors to do with the patient. Often it is more than one factor that leads to inadequate adherence. In Chapter 3 – Clinical consequences of non-adherence – these five factors are explored in depth. However, it is important to consider all possible influences when assessing adherence, and plan interventions accordingly in a targeted and comprehensive manner to assist the patient with respect to his particular needs.

If one supports a patient’s adherence to the recommended and agreed-upon therapy, this leads to sustainably successful treatment. In case of non-compliance with recommendations, the patient can experience life-threatening complications or risks, such as:

- Recurrences that are difficult to treat and potentially fatal
- Increased risk of dependence on the health system and, consequently, lesser quality of life for the person affected
- Increased risk of the disease developing resistance to treatment
- Increased risk of unwanted toxicity / side effects of the drug (morbidity).

In addition, non-adherent behaviour can lead to considerable healthcare costs, which can be due to more frequent visits to the doctor or nursing staff, increased hospitalisation and longer hospital stays (Wu et al, 2010). In addition, a poor response to the
therapy can be misinterpreted by the patient as a failure of treatment, which may lead to inaccurate results with false conclusions in clinical studies (Ibrahim et al, 2011; Marin et al, 2010).

The relationship between the benefits and risks of adherent behaviour is shown in Figure 1. Not every patient sees the same benefit in therapy or recognises the risks of therapy if behaving non-adherently. Not everyone can make the connection between these two components of therapy.

Figure 1: Effects of adherence on therapy (Novartis)
1.4 Implications for practice

What are adherence / non-adherence in relation to patient safety in clinical practice? Indeed, must nursing personnel address this question at all, or can we leave it to other healthcare professionals? Who should feel responsible for discussing contributing factors and how they correlate with the patient and his family searching for solutions? It seems reasonable that this problem should not necessarily be handled by only one professional group but by all who are in direct contact with the patient and his family who can work together with them on the challenges they are facing (see Chapter 5 – Patient / family education). This means that there must be a continued commitment to adherence by all concerned. Only through support that is constantly available and used continuously can the patient’s needs be met.
2 Theoretical concepts

Various concepts can help us understand the phenomenon of adherence/non-adherence and derive interventions from it. To influence non-adherence, it is necessary to understand the patient's behaviour and the background that leads to the relevant behaviour. Only this can direct the team toward behavioural changes and support the patient suitably. Motivation, based on the acceptance of therapy, is as important a component as learning habits or changing habits to approach the goal of adherence. The following gives brief insight into different theoretical models that can serve as a basis for behavioural changes and focus on the intention, self-motivation and selfefficacy of a person.

2.1 The Health Belief Model (Rosenstock, 1974)

The Health Belief Model (Rosenstock, 1974) was originally developed by researchers at the U.S. Public Health Service in the 1950s. Its goal is to find an explanation for why people initiate a preventive measure or not. The model comprises the following possible factors:

- Considerations that one bears a (potential) risk for a disease or a negative outcome.
- Considerations as to how difficult a particular disease or the negative result is if it then actually occurs.
- Considerations as to whether the recommended treatment is effective or whether a change in health behaviour is reasonable and achievable.
- The belief in how well a person himself is managing to address the challenges to ultimately achieve and maintain health.
Demographic characteristics (e.g. age, gender) and environmental influences that might motivate a person to do something in a positive direction are other aspects of this model (see Figure 2).

![The Health Belief Model](image)

The Health Belief Model shows that both patient factors and environmental factors contribute to whether or not a patient adheres to the recommended therapy. After 1988 the concept of self-efficacy (the belief that one is able to initiate a change) was added. This model shows the factors that contribute to understanding why it is necessary to adhere to agreements that have been made. This can then be addressed in discussion. Based on an appraisal of influencing factors, the likelihood of the success of the behaviour can be assessed.
2.2 The theory of reasoned action / theory of planned behaviour (Ajzen & Fishbein, 1980)

The idea that a person’s behaviour is guided primarily by intention was developed in the 1970s. It is among the most commonly used approaches for predicting and explaining health behaviour (Ajzen & Fishbein, 1980).

This model (see Figure 3) assumes that a certain attitude dominates a person’s feelings. A change in attitude can bring about changes in behaviour, because all behaviour-based decisions are ultimately based on faith in something. Moreover, the behaviourally based intention of an individual is controlled by the relative importance of the attitude toward the behaviour of the individual and steered by subjective standards. Intention is the most important proximal predictor of behaviour. Intention, in its turn, is predicted by attitudes, the subjective norm and the perceived behavioural control.

![Figure 3: The model of the theory of reasoned action / theory of planned behaviour](image-url)
The theory of planned behaviour, which is complementary to the theory of reasoned action, also integrates the concept of perceived control over the opportunities, resources and skills necessary for activating the behaviour. This is a core element of the self-efficacy concept of Bandura. This model, too, provides structure for the behaviour of the individual concerned and appeals to authoritative areas that contribute to adherent behaviour.

2.3 Transtheoretical Model of Change (Prochaska & DiClemente, 1982)

(Pre-contemplation – Contemplation – Preparation – Action – Maintenance – Termination)
Originally the trans-theoretical model of change concerned the process of change in psychotherapeutical treatment. It quickly became clear, however, that behavioural changes are not only observed in the psychotherapeutic setting, but also in general health behaviour. The core of the model includes six stages of behaviour change (“Stages of change”; see Figure 4):
1. No intention exists in the stage of “pre-contemplation” – there is a lack of intention to change problematic behaviour.
2. In the stage where an intention is being established (“contemplation”), people intend to change problematic behaviour at some time.
3. In the next stage (“preparation”), people actually plan to change problematic behaviour soon and undertake the first steps toward a change in behaviour.
4. In the action stage (“action”), people change their behaviour.
5. In the maintenance stage (“maintenance”), people have abandoned the problematic behaviour for an extended period.
6. In the final stage, the person can maintain the behaviour (“termination” or “stable behaviour”).
The 6th stage is not contained in the original literature of Prochaska and DiClemente. It was added later by other authors. It is important to note that a change depends on what stage the person is in. To progress from one stage to the next, non-imperative effective strategies from the next higher stage must be applied. In addition, as a rule the various stages do not run linearly; indeed one shifts constantly between the different stages.

*How can I tell whether a patient is ready to initiate a change?*

If a patient is aware of the problem and sees the benefits of his efforts but has no concrete plan yet to change behavior, she needs more useful and practical information at her level of understanding. Only when a patient develops an awareness of the problem is she actually willing to accept support to tackle the problem in concrete terms.
2.4 **Model of Information – Motivation – Strategy**  
(DiMatteo & DiNicola, 1982)

Before a person shows a change in behaviour he must know (1) what changes are necessary (information based on “health literacy”, knowledge, belief in the therapy or memory) and (2) have the desire/see the need for changing behaviour (motivation based on attitudes, feelings, trust and expectations). Finally, (3) the necessary tools and resources must be activated (strategy with behavioural skills, based on financial and practical resources such as time and social support) to achieve this change in behaviour and sustain it. This model (see Figure 5) is very flexible and can therefore easily be used as the basis for new techniques and strategies for improvement of adherent behaviour (DiMatteo, Giordani, Lepper, & Croghan, 2002).

![Model of Information – Motivation – Strategy](image)

*Figure 5: Model of Information – Motivation – Strategy*
2.5 Health literacy (Kickbusch, 2001)

Health literacy is usually referred to as “knowledge-based, social and cultural competence for healthy lifestyles” (see also Abel & Bruhin, 2003). This model (see Figure 6) assumes that the patient must be sufficiently “trained” or educated to be able to carry out the therapy. It describes the individual abilities needed to obtain and understand the information necessary for the individual situation. Health literacy encompasses three different levels (Nutbeam, 2000): the functional, interactive and critical level.

![Figure 6: Health literacy](image)

Although the reading skills and general knowledge of a person are related to his health literacy, better-educated people do not necessarily have a higher level of health literacy. Professionals consistently overestimate a patient’s level of knowledge and use terminology that the patient often cannot grasp or understand.
In patient education with regard to adherence, all three skills (functional, communicative and critical health literacy; see Figure 7) of the patient are addressed to determine which skills the patient lacks and which need to be trained accordingly.

2.6 **Self-efficacy / self-regulation (Bandura, 1977)**

Behaviour, environmental influences, cognitive and biological or other personal factors may influence each other. Self-efficacy and self-regulation imply a belief that one can carry out the suitable action in a particular situation.

This feeling a person has about his skills influences his perception, motivation and performance in many ways. The assessment of self-efficacy depends on (see Figure 8)

- one’s own actual performance
- observations of the performance of others
• osocial and self-directed convictions (others can convince us that we can do something ourselves, or we convince ourselves)
• the observation of our emotional states while we think about a task or dare to commence one
Positive expectations regarding self-efficacy can be generalised to new situations.

If one looks together with the patient at his ability in terms of self-efficacy, it is possible to see together whether the expected result and the existing social structures lead to his goals, which are ultimately the basis of adherent behaviour.

Figure 8: The model of self-efficacy / self-regulation
2.7 Summary

- Different theoretical concepts can be used to understand the patient’s behaviour in the context of adherence, and to accompany him supportively depending on the nature of the problem.
- It may be helpful to assess the various dimensions in which the patient moves and work with her to determine which factors can be modified to achieve the goal of adherence.
- The consideration of all dimensions and factors can contribute to the patient feeling that he is being taken seriously and is prepared to change something about his behaviour. At this time, unsuspected resources can be appealed to and activated that are consistent with the person, his lifestyle and his socio-intellectual background.
3 Factors influencing non-adherence

As you have learned in the first chapters, non-adherence in patients with cancer is a phenomenon that is more widespread than generally assumed. The clinical consequences for patients can be explained on the basis of five factors of adherence according to the WHO (2003) (see Figure 9). The consequences of non-adherent behaviour are not always symptomatic nor do they always mean a progression or recurrence of disease.

Figure 9: The five factors of adherence according to the WHO (2003)
3.1 Factors of the health system and the treatment team (Health System / Health Care Team (HCT) factors)

As you know, our hospitals and family physicians are mostly focused on acutely ill people. However, people with cancer need a health system that takes into account the chronic aspects of the disease (World Health Organization, 2001). Continuous medical care and independent patients who, together with their relatives, recognise the disease symptoms and act accordingly are two examples of this. A relationship based on a partnership between the patient, relatives and the treating physician improves adherence (Russmann, Curkovic & Huber, 2010). If, however, patients are inadequately trained to understand their treatment, undesirable effects caused by incorrect or inadequate medication intake (e.g., by the inadequate use of anti-emetics in cytostatic therapy) may lead to decreased quality of life, more frequent physician consultations, and even rehospitalisations (Ruddy, Mayer & Partridge, 2009). Patients with chronic pain, for example, need a doctor less frequently if they know their basic pain management and can deal independently with the reserve drugs. If training is offered, it is also recommended that relatives or trusted persons proposed by the patient be instructed.

All members of the treatment team must be aware of the importance of adherence and how to seek dialogue with patients and their relatives to develop joint strategies (Schäfer-Keller, Garzoni, Dickenmann & De Geest, 2010).

Cancer patients are often cared for not only by a treatment team, but also by several doctors, nursing personnel and other persons in the health sector. The complete provision of information to all parties concerned facilitates efficient, effective and targeted support (Barefoot, Blecher & Emery, 2009).
Spengler (2010) mentions the importance of pharmacists in transplantation medicine. Different groups worldwide are working on the optimization of consulting, administering and using medicines and their side effects.

“Do you know of such projects in your country? How and where do patients receive medication after the hospital discharge? Does the patient always go to the same pharmacy? Does he get his medication from the treating physician or (more and more frequently) by mail order?”

For example, some pharmacies in Switzerland take on the important function of instruction on medications. However, this takes place in a less than comprehensive manner and with a less than optimal structure, which represents difficulties for persons with chronic health problems. It is our task to consider who can assume responsibility for this advice and support in the present healthcare system.
“Have you ever considered how patients must learn to take their medication management into their own hands?”

We usually assume that patients already know how to do things. Haslbeck notes in his book about drugs and chronic illness: “Do we assume that the persons concerned will now adapt their former lifestyle to the medication regimen or if necessary subordinate it thereto” (Haslbeck, 2010).

3.2 Socioeconomic factors

According to the WHO (2003), for cancer patients the long journey to the treatment centre represents a significant risk that they may be unable to adhere to the therapy as prescribed. Whether this occurs similarly in Switzerland remains to be clarified. Certainly it is difficult for patients living in rural areas to find a nearby pharmacy that can provide the right medications at any time. Similarly, travel expenses to the doctor as well as drug prices in Switzerland can be a financial problem. In Switzerland, for example, for medication and outpatient visits, each patient pays a federally established excess in the amount of 10% (up to an amount of 700 CHF per year), plus an elective health insurance excess. An additional burden may be represented by wage losses that can occur during inability to work due to acute illness. Reginster (2006) conducted a study of adherence in patients receiving bisphosphonates due to osteoporosis and its impact on treatment outcomes and health resources. It was noted, in 1986, that non-adherence in the U.S. caused $8.5 billion (€6 billion) in additional hospitalisations. At the same time an additional $17 to $25 billion (€12 to €18 billion) of indirect costs were incurred due to inability to work during hospitalisations (Reginster, 2006).

In a study of the working group Noens and colleagues (2009), adherence in people with chronic myeloid leukaemia (CML) was
examined. This showed that of 169 patients who were treated with the drug imatinib, only 14% of the patients took their pills completely adherently; 71% took less than the prescribed dose; and 15% indeed took more than the prescribed dose (Noens et al, 2009). Patients that behave non-adherently can thus mistakenly be counted as non-responders – that is, patients who do not respond sufficiently well to a drug, which is associated with an increased risk of disease progression. In reality, however, non-adherent patients did not take the prescribed dose of medications correctly. The reasons for this are varied. For example, changes in life circumstances that affect the daily routine of taking medication, or side effects, which lead them to "adjust" the dose themselves (Noens et al, 2009).

3.3 Health-related factors (condition-related factors)

The health of a patient can also affect adherence. Decisive here are a variety of symptoms with which cancer patients must deal: nausea / vomiting, pain, constipation, fatigue / weakness, and malnutrition to name a few.

Imagine a patient who is exhausted, for example due to cachexia, and suffers from chronic pain; he will have to take strong pain-killers, which might further increase his fatigue. This in turn can interfere with the proper execution of his treatment plan.

Most cancer patients are “experts” on their disease and know its symptoms and treatment very well. The progression of a disease can lead to a slow loss of independence, and patients become increasingly dependent on others.

This can reduce adherence, because it takes strength to organise help and willingness to accept it.
3.4 Therapy-related factors

Therapy-related factors refer to the taking and the number of prescribed medications. The therapeutic and drug plans of cancer patients are usually very complex. They require of the patients and their relatives concentration and precision to comply with all the directions. For example, certain medications must be taken before eating; others after a fasting period, while others require precise timing. If patients are travelling or working in shifts, carefully planning the daily program is important.

*How often do you talk to the patient or relatives about it?*

The drugs themselves have an impact on the patient due to their effects, side effects and interactions. We might think, for example, of patients who need to take their medication with food but feel will whenever they see food; or we need to think about the influence on the patient of the frequency, duration and number of tablets to be taken.

For drugs that have to be taken more than three times a day, adherence decreases significantly (Lee, Nicholson, Souhami & Deshmukh, 1992). Strong-smelling medicines can also hinder complete compliance. All of this affects patient compliance with the daily treatment plan. Do not forget to ask patients about experience with previous medication use.

Antibiotic therapy that was accompanied by severe diarrhoea or skin rash remains in the memory and may possibly make it more difficult for a patient to agree to a new course of antibiotics. Further caution is advised upon dosage adjustments that are ordered during routine follow-up or only orally on the telephone and not written down as a prescription. Caution is also advised with regard to speaking of progression of the disease to nonadherent patients and in the presence of growing disease parameters. This could
result in new cytostatic therapy being prescribed and a new phase of the disease and treatment commencing (Ruddy et al, 2009) although there might be other factors behind the progression.

3.5 Patient-related factors

An important factor is the patient himself. What is the attitude of the patient toward his illness and treatment? What does he want and for how long? What can he do? Who supports him in this?

Core questions are:
• What resources does the patient have?
• What is his level of knowledge about his disease, its treatment and prognosis?
• What is his attitude toward these factors?
• What expectations does he have?

Resources
Positive resources include social support from family or friends, physical and cognitive abilities, as well as being able to perceive success and celebrate it. Psychosocial stress situations, on the other hand, are among the unfavourable resources that can complicate the success of recovery.

Knowledge
Positive effects can be observed in patients who independently or with the assistance of the treatment team monitor their body and react to different signs / symptoms and can thus help themselves. Patients with a high level of knowledge about their disease and its treatment can question ambiguous instructions, decreasing the fear of adverse effects of therapy.
**Attitude**

If the patient has a positive attitude toward his illness, he finds it easier to come to terms with it, so his motivation increases to participate in regular monitoring by the medical team. Newly arising problems are re-evaluated by patients and solutions are sought. The motivation to continue fighting supports the patient on his way.

**Expectations**

If a patient expects to become healthy or to achieve a good quality of life, this helps him to cope better with the entire situation. However, if he expects negative effects from the disease or the therapy, he may indeed be less able to cope.

Figure 10 illustrates the complexity of adherence influencers.

### 3.6 Summary

- Non-adherence to medication intake in cancer therapy can lead to deterioration of the general condition and/or the prognosis.
- The reasons for this are varied.
- With knowledge of the possible causes, the treatment team can formulate therapy in a targeted manner, sensitising the patient and thus bringing about an improvement in adherence.
4 Methods of assessing and addressing non-adherence

To date there are no appropriate measurement instruments or methods that optimally detect adherence for each individual situation of a patient. In general, it is advisable to record the adherence of patients with different, complementary methods and repeat this regularly in the course of the chronic disease to keep track of the course. Thus one can distinguish between subjective and objective methods, or direct and indirect measurement methods. To date there is no golden standard that favours one method over another.

4.1 Objective methods

Objective methods include the measurement of the medication or its metabolites in body fluids, such as urine, blood, faeces or saliva. This method is often costly and complicated, since it requires the availability of appropriate laboratories and evaluation methods and quality controls.

One can also directly observe the medication intake. This method is used in other healthcare areas, such as in methadone programs – in oncology, this method is rather unusual.

4.2 Subjective methods

Subjective methods include patient and relative questioning, counting the tablets, and verifying the refill of prescriptions as well as electronic monitoring devices.

Patient survey (self-report): Patients are asked directly whether they have the impression that they can adhere to the agreed-upon
treatment. An indirect survey can yield a patient diary in which the tablet intake is recorded in writing. This documentation can then be discussed in an interview. Factors can be sought that led to the taking of, or failure to take, medications.

*Family survey (collateral report):* In certain situations it may be helpful to involve the patient’s support network in the medication use process. In a joint meeting it can be discussed what role the relatives have in supporting the patient in this process.

*Counting the tablets:* This method means that the patient brings the medication package to the next doctor’s visit and a joint check is carried out as to whether all the tablets were taken over the allotted period of time.

*Checking prescription refills:* This method must involve another professional group: the pharmacy plays an important role here, but only if the patient always goes to a particular pharmacy – if the patient orders the drugs over the Internet, it becomes more difficult.

In addition, when a new long-term prescription is given, we could check whether the time period between two prescriptions is correct and assess if it was too long or too short.

*Electronic Monitoring Device:* This method requires a special medication container that has a lid with an integrated chip. This chip registers any opening of the container, where it is assumed that the patient then actually takes the medication. One difficulty involves checking of multiple doses, that is to say when the patient must take two or more tablets per instance, which is not registered by the chip.

This method has already been used for quite some time with cancer patients in clinical practice (Lau, Matsui, Greenberg & Koren, 1998; Marin et al, 2010).
4.3 Criticism of collection methods

All methods have advantages and disadvantages that should be weighed carefully against the clinical benefits. The measurement of the drug or its metabolites in body fluids depends on the absorption of the drug — the metabolism can be very individual. It goes without saying that the direct observation of medication intake in a home setting by professionals is not feasible in the long term — one cannot always stand behind the patient and check whether or not he actually takes the medication. This responsibility could be taken over by family members. This can, however, represent a burden in the relationship between the patient and the family member.
Responses of patients and relatives can be erroneous or, depending on the situation, distorted by social desirability. In this situation, open communication in the relationship between patients, relatives and professionals is essential. However, the patient can deceive both professionals and family members with respect to medication intake.

Counting the number of tablets or checking that the prescription is filled does not guarantee that the patient actually takes the pills accordingly. This method also encounters limitations if the patient does not always have his prescriptions filled at the same pharmacy, orders medication over the Internet or forgets to take his medication boxes with him to the next appointment. Such situations make the monitoring of adherence difficult. Patient diaries can help to identify critical situations in medication taking and find a suitable solution together with the professional staff.

Electronic monitoring devices are often bulky, which is inconvenient for some patients if they must take the medications while travelling. The same is true for liquid medications or with drugs that should be kept for as long as possible in their blister packs. The installation of the computer program and the subsequent data transmission and analysis can also be time and cost-intensive.

4.4 Intervention possibilities

All strategies for supporting adherence must be both reliable and valid. We know that the behaviour of the patient depends on her motivation, belief in health and habits. Only if we are aware of them we will be able to find specific points that we can use to change behaviour (Lehane & McCarth, 2009). For example, all intervention offered must always be variably and continually adapted to the individual situation of the patient.
We now know that changes in habit are only sustainable if – even after a long period of time – one stops, evaluates the situation, and makes relevant adjustments that lead to increased attentiveness to adherence.

Depending on the factors that play a role in an individual situation, achieving a sustainable effect requires a combination of intervention strategies that are supported and applied by all persons involved with the care of the patient. After screening for risk factors, a combination of patient education, behaviour modification strategies, supporting self-management strategies and telephone follow-up is promising. It is essential that the social network of the patient is involved. It is important to determine whether the social network needs assistance – whether they understand the information and discuss with the patient how he can change his habits so that he can incorporate the intake of medication into his daily life.

Figure 12: Multidisciplinary collaboration (Ref: Monica Fiedner)
Collaboration between physicians, nurses, psycho-oncologists, pharmacists, families, patient groups, drug companies and many other professional groups is essential in supporting the patient (Figure 12).

Depending on the risk factor that plays a role in non-adherence, it may be useful to refresh the patient’s knowledge. Here patient education plays an important role. The bases of the assessment of the situation are the so-called “5 A’s”: Ask, Advise, Assess, Assist and Arrange. These structural components can be helpful in patient education. Patient education is only useful if you have selected a good time to convey to the patient in an appropriate manner, with the best teaching method, what he needs in his situation. Ideally this should include his social network as often as possible. It is generally known that depression may play a role in non-adherence – it is very important to treat this psychological disorder professionally.

If a patient is suffering from symptoms of the disease or side effects of medication, one should work on interventions with him so that he can deal with them on his own when at home or know where to turn to in case of uncertainty and questions. Professionals must be aware of side effects and support the patient accordingly (Winkeljohn, 2010).

If the patient has a weak social network, it is advisable to discuss this with her and possibly encourage her to obtain the necessary support from people she trusts. Patient organisations may also play a supportive role here.

Financial constraints should be openly discussed with the patient. It is possible that the patient can no longer afford the medication because of the high franchise / percentage share some patients have to pay.
The professional should address this and a viable solution should be sought in consultation with available services.

If **forgetfulness** is a factor, various support tools or memory strategies may be helpful. Helpful tools can be found on the Internet (e.g. www.patientcompliance.net; www.epill.com; www.forgettingthepill.com). Also, there are now reminder services via SMS. Depending on the medication, it may even be offered free (www.memorems.ch).

Possible interventions should be evaluated (see Chapter 6 – Evaluation). An evaluation can make the success of the intervention visible or be used to determine new goals.
5 Patient/family education

As a result of demographic trends, the growing number of patients and changing family structures, training and advice for caregivers and patients is an increasingly important area for nursing personnel.

Training and consultation in the nursing sector already takes place quite frequently, but usually randomly, and often it occurs too late and is rarely custom-made (Zegelin-Abt & Huneke, 1999).

If, on the other hand, you consider advice as an area of responsibility of nurses, it becomes a factor on which care is defined. Pay attention to how often you informally impart knowledge while doing nursing work. For example, you answer questions from your patient, prepare him for a nursing procedure or explain the purpose of a medical device.

If you recognise these moments as teaching moments and above all realise how you can explicitly count these and document them as nursing care, you will need no “time for training”. The first step consists of consciously perceiving the educational services that you constantly provide.

5.1 Is education cost effective?

An analysis of various studies on the costs and benefits of patient consultation came to the following conclusion: On average, every US dollar invested in patient advice yielded a saving of three to four US dollars. None of the studies came to the conclusion that advice costs more than it saves (Bartlett, 1995). So – counselling patients and family members pays off. It is imperative that we tell our patients what is happening to them and guide
them to care for themselves. Consultation is the most important tool for cost containment and knowledge is the most important therapeutic intervention.

In the calculation of staffing needs, it would be worthwhile to consider the time that is necessary for such measures.
It is important to sensitise and qualify nursing personnel for the training and counselling of patients and their families.

To conduct effective training, this must be based on a concept that can be tailored to actual implementation in an individual situation.

5.2 Process of patient and relative education

Patient education comprises the process of diagnosis and intervention. In the assessment phase, the type of need and motivation to learn is determined and goals are formulated together with the patient. Intervention involves stimulating instructions exactly customised to the learning needs of the patient/relative. The implementation is evaluated throughout the training process. Learning content must be repeated frequently, because it is not exactly predictable which of the explained concepts will lead to the desired learning effect in a patient.

The training process can be viewed as one similar to the nursing process, because both include the phases of assessment, diagnosis, goals, intervention and evaluation.

The most common errors in patient education include the failure to identify learning needs so that no training takes place, and the omission of one of the possible steps within the education process.

The advice should enable the patient / family to:
• take adequate and carefully considered decisions
• develop or maintain vital self-care skills
• identify problems and respond suitably to them
• obtain answers to questions and find the right contact person

Patient education is generally designed in such a way that the conditions that promote learning are ensured: Start with the objectives, involve the goals of the patient and keep an eye on these from the time of planning through the time of evaluation.
• Ask the patient about his previous experience with taking medication. In what areas did he manage to do this well, where were the difficulties?

The goals of advice are action-oriented. They all serve to answer the fundamental question of the patient: “What can I do?”

The long-term goal of patient counselling is to help the patient / relatives achieve healthconscious thoughts and promote action. To achieve this, however, first the short-term objectives must be achieved:
• Establish training measures in line with the skills, knowledge structures and expectations of the patient.

Be sure to express yourself clearly. Check whether the patient has understood what and when he should do something or refrain from doing it. Only give as much advice as is useful. Some patients tend to be intimidated by too many technical terms:
• Set realistic tasks that the patient can perform competently in time and which he also believes he can perform.
• Provide organisational assistance in the form of brief learning overviews to give the patient an idea of what to expect.
• Organise complex information in easily memorable structures (graphs, diagrams).
• Use different teaching methods because patients prefer different learning styles (auditory, visual). Use the method that appeals most to the patient / relatives.
• Give the patient feedback at the next visit, so that he feels reinforced and can improve himself where necessary – in this way he knows where he stands in the learning process.
• End the training by having the patient repeat what was learned and observe how he utilises what he has learned in actual situations (reflection).

5.3 The role of relatives in connection with patient education

Family members or caregivers of patients, when possible and with the patient’s consent, should first be informed that they should play an active role in the interest of the health of the patient. You can call the partner or the patient’s family and speak to them directly as to their expectations and how you wish to involve them. It is important that you identify common goals and attune your educational measures accordingly. You can agree on a fixed date for consultation with the relatives.

If the relative cannot come to you, you can send him the advisory material and discuss this by phone. Exchange ideas with colleagues and document all steps of planning, counselling efforts and learning success (Hartigan, 2003).

5.4 Exploiting educationally favourable moments

The ideal moment for advice is when the patient asks a question or carries out a healthrelated procedure. During such a moment the issue is clearly defined and the patient is highly motivated.

This was also shown in a study that concluded that “… the information patients receive is distributed too unequally … Patients were given too much information on the day of admission, while
upon discharge they were given too little information (Breemhaar, van den Borne & Mullen, 1996).

If we were to look for educationally favourable moments upon every interaction with patients and families, we could distribute the information better. In addition, it would also reduce the pressure placed upon us if the entire consultation were not postponed to the last minute, but distributed over time. Because a motivated patient learns best, one could also expect more success in the establishment of goals.

Here are some examples of educationally favourable moments:
• When the patient asks a question.
• When the patient makes a provocative statement, such as: “Things like this happen to me all the time.”
• When you hand out medication. Explain what it is and what it does.
• If you see something on TV with the patient that is related to his situation, establish a discussion based on what was seen.

Consulting also means to create circumstances in which learning is possible (Redman, 1993).

However sometimes one does not succeed in finding an entry to convey essential information to the patient. Perhaps basically he does not care at all whether his medications have side effects. Nonetheless it is urgently important that he knows that dangerous or unwanted side effects can occur and what he should do if this happens. Your task is to bring about the conditions for the learning process.
5.5 What are the needs of the patient?

There may be times when you have patients who refuse therapy or do not want any information. But these are isolated cases. These patients prefer to know nothing and prefer not to take any responsibility. Far more often there is a negative attitude, because despite all your best efforts you were not able to establish a cooperative alliance with the patient.

Various studies (e.g., Esposito, 1995; Furlong, 1996) were able to show the relationship between knowledge and compliance. It was found that knowledge had a positive impact on the motivation for therapy, even if the behaviour of the patient was not predictable in each individual case. Patients usually want information and want to be involved in decision making (Merkatz & Couig, 1992).

Patient counseling is an ongoing process. It views the patient holistically with all his needs and concerns, and works with him to establish joint goals. The consultation process also includes the evaluation of what is learned, the use for the patient as well as the ease with which the patient has established his self-care practices (Rankin & Stallings, 1996). The concept of patient education delineates only a small part of the consultation process: the instantaneous dissemination of information to the patient.

5.6 Avoidance of unnecessary repetition

Review the documents on what educational measures have been documented by other team members. Check to see to what extent the patient has understood the information provided so far, and go from there. Clear up misinterpretations and misunderstandings immediately. If applicable give the patient the necessary details.
If you feel resistance in a patient against your educational efforts, you should immediately stop and reassess the situation. Sometimes it is impossible to awaken an awareness of the problem in the patient simply by providing information on behavioural changes.

Respect the right of your patient to reject recommendations, be it for the moment or permanently. Maintain an atmosphere of respect, open communication and constantly available information, and secure optimal self-care.

A disturbed relationship between you and the patient may make it necessary for you to step back and allow another member of the care team to take over the consultation.

Learn to recognise such moments and react accordingly.

### 5.7 Typical errors

Do not ask: “Do you have any other questions?” If the patient answers “no”, all further discussion ends. Instead, ask: “Could I have explained something better?” Through this question, you take responsibility of the individualisation of the advice.

Do not give the patient the impression that it is forbidden to interrupt you.

- This excludes the patient from the consultation process.
- Consultation proceeds most effectively and quickly if it is based on a dialogue.

Do not treat medical information as dogmatic belief, but as knowledge that is indeed scientifically based but can nonetheless be challenged. The total continuous process of consultation is much more important than simple instruction.
The mere imparting of knowledge, as this takes place in the context of current patient education, certainly does not guarantee any behavioural change. Effective patient and family counselling is only possible if communication and cooperation between the individual members of the nursing team functions.

5.8 Written information

To achieve effective consultation, oral communication should be combined with written documentation. While oral communication is best suited for the provision of information, simple written documents can help emphasise the information given orally (Mayeaux et al, 1996).

Written information materials have the following advantages:
• They are standardised, so each member of the nursing team provides the same content.
• They are available to the patient as a lasting source of information.
• They can be updated quickly and easily if you have created them yourself.

However, written consultation documents have the following disadvantages:
• The patient must read and be able to understand what is written.
• It must be appropriate for the patient (content, culture, language, reading skills).
• It must be available at the right moment.
• The storage and reordering system must function.
• Always clarify costs and payment in advance.
5.9 Active involvement

According to Doak and Root (1996) the effectiveness of written material is increased if tailored to the individual patient.

Highlight or underline key points as you discuss them, or have the patient do this. Write the name of your patient on the document and give him a pen. Explain to him that he can and should make notes with the pen if it helps. Then you can review the information with the patient or ask him to wait before reading it until you speak with him about it.

A question-answer format and bullet points makes the text clearer (Masset, 1996).

Photos and illustrations loosen the text, but must be chosen with care and deliberation. Furthermore, authors of texts must adhere to the following guidelines:

- Key messages must be positioned visibly.
- The first paragraph lists the main advantages and necessary activities for the reader.
- The task to be managed is described step by step.
- Address the text directly to the reader. Thus facts are conveyed in a personal way.
- Communicate content in a way that respects the cultural background of the readers for whom it is intended. Include appropriate lifestyles, cultural characteristics and symbols.

Most studies on the subject of “readability” come to the conclusion that many patients who rely on written educational materials only understand them to a limited extent (Klingbeil, Speece & Schubiner, 1995).

The term “readability” refers to how understandable written texts are. The readability formulas relate to how easy a text is to read and not whether it is easy to understand. Such characteristics as organisation (headings, overviews), suitable order and clarity,
which are also not included in readability formulas, are just as important to written and other educational materials.

Graphic guidelines for easily readable and well-written texts (from Buxton, 1999):
Draw the reader’s attention to the message.
• Arrows, underlining, bold or italics, boxes, bulleted lists to draw the reader’s eyes to the key messages.

Select a readable print.
• Font size 12 to 14 points.
• Good legible font: Serif font (such as Times New Roman) in continuous text.

Create a readable text.
• Lines with 40–50 characters, left-justified.
• High contrast for text and background, such as black on white.
• Sufficient line spacing.

Add images with a clear message.
• A key message for each image; put the message in the legend.
• Express the message so that it is immediately understood.
• Realistic drawings, photos or human-like figures.
• Images that the reader can relate to easily.

5.10 Training concrete population groups

The educational needs of specific population groups with cancerous diseases require particular attention. 50% of all cancers occur in people older than 65.

The educational needs of this age group have thus far received very little attention. Written and oral information should take the perspective of this group of patients.
If the national language is not the native language of the patient and you do not know that language, communication problems can pose a significant obstacle to patient and family counselling (Chachkes & Christ, 1996; Westermilie, 2004).

Even in patients and relatives who under normal circumstances can communicate very well in their second language, it happens that in stressful situations they can only communicate in their native language (Chachkes & Christ, 1996). In patients who understand the national language insufficiently, it is imperative to consult an interpreter. If written information is available in the native language of your patient, you should use this.

As with any patient, it is important to check whether what was read was understood. If possible use bilingual texts, so that the interpreter or the family member that knows the national language can help the patient in understanding the content. Furthermore, it is important that you respect the beliefs, habits, values and traditions of the patient. You should also work in a “culturally correct” manner. In some cultures, directives are perceived as offensive; in others a direct approach is expected. Admit it if a culture is alien to you, and apologise if you have committed a faux pas.

5.11 Telephone follow-up programs

As part of the routine follow-up after a hospital stay, for example telephone-based contacts, is recommended (Holmes & Lenz, 1997).

Patients need time to process new information. Information that still appeared to be unclear at the end of the consultation can quickly seem meaningless at home. Suddenly, problems arise
that no one has foreseen. Telephone follow-up programs not only increase patient satisfaction, but are also an effective means to enhance educational continuity. Thus, in recent years follow-up programmes have been developed and tested in which specialised nursing personnel support the patient after clinic discharge or subsequently on the phone, coordinating the relevant nursing care (e.g., Ades et al, 2000; DeBusk et al, 1994). The benefits of telephone follow-up are obvious: In addition to the relatively low costs of space and travel, this form of follow-up is distinguished by its high degree of flexibility and adaptability to the needs of patients. Another advantage is the possibility of specialisation of the nursing staff in this form of follow-up care. A professional nursing employee can therefore take care of many patients with the same disease and comparable problems without any geographical limitations.

Tell your colleagues who are responsible for telephone follow-up which points worry you most about the patient. Then, potential problem areas can be evaluated specifically. The financing of telephone follow-up must be clarified in advance, because in many countries there is no possibility of settling this with insurance.

5.12 Primary nursing education and continued education

Smaley (1997) found that many nurses receive no formal training in patient counselling and have never heard anything about proper consultation documentation.
5.13 Learning style

In the 1970s the psychology of learning established the concept of learning styles. It assumes that we rely mostly on a few individual methods in the processing of information. This accounts for the differences in the learning achievements of various individuals under the same conditions, if only one learning method is offered. In recent years, particularly teachers have been advised to adapt their teaching methods to the learning styles of students (from: www.de.wikipedia.org/wiki/Lernstil).

Visual, auditory and kinaesthetic learning
Since the seventies over 80 different learning style models have been proposed. The group of Felder & Silvermann places particular emphasis on sensory impressions during information processing (Felder & Silverman, 1988). There are four basic types.

The visual type
The visual learner learns best by reading information and observing actions. He finds it easier to memorise content if he can view this in the form of graphs or images. The visual learner likes to read, and to look at pictures, illustrations or graphs to understand facts. He needs a good learning environment and enjoys working with panel paintings and written documents. He enjoys joining in the writing and absorbs information by seeing and being shown. He particularly remembers what he himself has read and seen.

Tip: Draw mind maps, pictures; work with coloured pencils or markers.
However, this learning type can be easily distracted by visual confusions.
The communicative type
The communicative learning type learns best through discussions and conversations. For him, a verbal confrontation with the subject matter and understanding in dialogue is of great importance. The communicative learning type must have an issue explained to him and discuss it in detail in order to understand and remember it.

The auditory type
The auditory learning type can easily absorb information that he has heard, retain it and repeat it. He can follow verbal explanations and processes them. Explanations sound coherent to him; he can comprehend to it, they sound appropriate. The auditory learning type learns best when he hears the teaching materials (e.g., on educational tapes), reads the text aloud for himself or listens to another person reading it. He is very good at learning by heart when speaking out loud; verbal tasks are easy to him. Auditory learners are easily disturbed by ambient noise and usually want no music in the background.

The kinaesthetic type
The kinaesthetic learning type learns best by actually performing action sequences and comprehending them in this way. For him, it is important to be directly involved in the learning process and collecting his own experiences through “learning by doing”. He understands explanations; they feel right. He explores topics and processes them. This type learns best when doing something himself, for example, through experimentation, role play and group activities.

Independently of your preferred learning methods, try to include as many senses in your learning process as possible – the more diverse the ways by which we learn material, the more varied the ways of remembering and retaining.
Therefore recollection increases the more senses are involved in the learning process:
• Only hearing 20%
• Only seeing 30%
• Hearing and seeing 50%
• Seeing, hearing and discussing 70%
• Seeing, hearing, discussing and involving oneself 90%
(from Felder & Silverman, 1988; Honey & Mumford, 1992; Kolb, 1985)

5.14 Frequently asked questions

How can I quickly assess the learning style of a patient?
The quickest way to determine the learning style of a patient is by asking, “The last time you wanted to learn something, how did you proceed?”

How can I quickly assess the educational success of a patient?
You can do this best by asking the client to demonstrate to you or repeat in his own words what you have taught him.

How do I assess the patient’s willingness to learn and how do I get someone to learn something when he is not yet ready for it?
In educationally favourable moments, the willingness of patients to learn is high. This is demonstrated by the fact that, for example, he makes a provocative statement (“I cannot possibly remember when to take all these pills”).
The better you learn to recognise educationally favourable moments, the stronger you will become aware of how often your patients are actually ready to learn.
You can increase the willingness to learn of patients and their families by steering them gently in the right direction.
How do I involve patients and their relatives?
Direct talks are the best way to actually involve the patient in the counselling process.
Find out what he already knows, what he needs to know and what he wants to know.
Find out what makes him worry. Set common goals.

How do I best deal with patients who do not speak our language?
If a patient does not speak the national language, it is best to consult an interpreter.
It is also useful to have written documents in the native language of the patient, which can be accessed later by him or a relative that is able to read.

I’m often not sure how detailed I should be about possible side effects of the medications, because I do not want to unsettle them unnecessarily, but do want to inform them well. Do you have a tip?
Build on discussions, interactive approaches and professional assessments.
For example, make a file on side effects. Print out a list in table form on which the most common side effects are listed, glue the list onto a piece of cardboard and cut out small cards, one for each side effect. Sort the cards into a box that you keep in the medicine room.
Also ask the patient how he will react if he has any of these side effects. Which can he deal with himself? Which require medical care or observation? Which need an immediate action?

How can we get doctors to support our educational efforts?
Doctors do not always like it when we tell or ask their patients too much.
Instead of starting with consultations and then asking doctors to contribute, get together as a team and design the relevant measures jointly.
If the other members of the care team are part of this process, they will automatically cooperate. Talk to them about the benefits of patient and family counselling. It may be necessary to encourage the patient to request information and motivate the doctor in this regard (from Hartigan, 2003; Klug-Redman, 2009; London, 2010, Rankin & Stallings, 1996).
6 Evaluation and clinical studies

For you as a care professional, it is of great importance in daily practice to find access to studies. Especially in patient education and when it comes to adherence, the verification of acceptance and the use of patient and family education as well as intervention through an evaluation are essential. The aim of quantitative research is to test and compare nursing interventions, medications or other treatment modalities. Depending on the stage, these studies are often characterised by a large sample size. The goal of qualitative research, on the other hand, is to understand phenomena in nursing and other disciplines of social science. The sample size is usually small because the interesting features are often collected through observations and qualitative interviews.

The following sections give a brief introduction to key concepts and steps in the planning, implementation and evaluation of clinical studies.

6.1 Evaluation studies

In evaluation research usually the value or benefit of a program, treatment or practice is systematically evaluated, assessed or analysed (see Kozar, 1999). Evaluation research shows what leads to the desired or useful result and what does not. Studies that examine evaluation can be both formative and summative in nature; mixed forms are also frequent as well. Formative studies examine the implementation of a program and primarily evaluate the process of a programme, while summative studies evaluate the results. It is important to note that results of evaluation studies are valid only for the specific situation and thus cannot be generalised (Sullivan Bolyai & Grey, 2005).
Studies on the evaluation of education or intervention measures on adherence in patients with an oncological disease are still rare today.

**An evaluation can pursue the following objectives:**
- The development of programs (including design and development of planned measures).
- Supporting research, i.e., the ongoing monitoring of the implementation and execution of a program.
- The assessment of benefits and effects of a program, i.e., the assessment of whether and to what extent the program has effected a change in the desired direction, or the designation of the degree of goal achievement, efficiency assessment or cost-benefit analysis (see Görrès, 1998).

### 6.2 Phases of a study (Schumacher & Schulgen, 2008)

Each scientific study is based on a research plan (proposal) that must always be presented to an ethics committee if people or animals are involved. In general the study plan is formulated after the exploratory phase. The individual steps of a study are presented below (see Figure 13).

**Exploration phase**
At the beginning of the study, based on a systematic literature search in major databases (e.g., PubMed: http://www.ncbi.nlm.nih.gov/pubmed/ and CINAHL: http://www.ebsco-host.com/cinahl) the researcher should acquire the latest knowledge on the research topic. If possible, there should be a discussion with competent experts on the point and necessity of the proposed study.
Theoretical phase
In the theoretical phase variables to be examined are put into a relationship and a question with hypotheses and objectives is formulated. The question should be embedded in a theoretical framework. Thus the hypothesis is substantiated theoretically and deducible. No study planning should be started if the exact question and its measurement variables are unknown. This is one of the most important preconditions for research work. Because, however, a theory in medicine is never complete and therefore the reality cannot be adequately and precisely described in all details, the hypothesis to be confirmed must be verified empirically. Once the questions and hypotheses are formulated a research plan is developed that contains all relevant information about the study aims, the variables to be examined, the methodology and the required study participants, and the advantages and disadvantages or limitations of the study. Before the study can be conducted, the study underlying the research plan must be registered and approved by the competent authority and/or Ethics Committee.
Collection of data
After approval of the study, the participants are recruited and the study is carried out. Regular monitoring and checking the data for accuracy is essential in this phase.

Analytical-statistical phase
In the analytical-statistical phase, the data are analysed by means of biostatistical methods. In retrospective studies, the data have usually already been documented and must be prepared and analysed in an appropriate manner.

Interpretation of results
If the results of the statistical analysis confirm the theory, the correctness of the hypotheses derived is checked. The results can now be distributed by embedding them in a scientific publication or in a theoretical framework and discussing them in a broader context. The final results of a study typically serve as the basis for recommendations for practice (see Table 1).

<table>
<thead>
<tr>
<th>Phases of a study</th>
<th>Components of a phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploration phase</td>
<td>Review of the literature, discussion with experts, etc.</td>
</tr>
<tr>
<td>Implementation phase</td>
<td>Recruitment of study participants Implementation of the study Monitoring and Data Management</td>
</tr>
<tr>
<td>Analytical-statistical phase</td>
<td>Planning, data collection, description and analysis</td>
</tr>
<tr>
<td>Interpretation of the results</td>
<td>for or against the hypothesis, dissemination of the results, recommendations for practice</td>
</tr>
</tbody>
</table>

Table 1: Components of the planning of an epidemiological study
6.3 Types of Studies

Depending on what target scopes are relevant to the study, a distinction is made between risk, diagnosis, prevention, treatment or prognosis study. Table 2 gives an overview of the various study types and their influencing and target variables.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Influence variables (independent variables)</th>
<th>Target variables (dependent variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk study</td>
<td>Risk factors (e.g., environmental factors, genetic or behavioural factors)</td>
<td>sickness, death</td>
</tr>
<tr>
<td>Diagnostic study</td>
<td>disease status</td>
<td>result of a diagnostic test</td>
</tr>
<tr>
<td>Prevention study</td>
<td>Preventive measure (vaccination or screening)</td>
<td>disease</td>
</tr>
<tr>
<td>Therapy / Intervention study</td>
<td>therapy form (medication, surgeon, procedure, therapy, intervention)</td>
<td>Effect of a Therapy / Intervention</td>
</tr>
<tr>
<td>Prognosis study</td>
<td>Disease or other prognostic factors</td>
<td>Final condition (cure, remission, progression or death); time to occurrence of an event</td>
</tr>
</tbody>
</table>

Table 2: Study types

6.4 Study designs in research

In the planning of studies one should have detailed knowledge about the various study designs. The design has an influence on the planning, implementation, analysis and interpretation of study data. Below is a listing of the most common study designs in research.
Descriptive studies
Descriptive studies are purely descriptive. The data are analysed without the option of deducing temporal or causal relationships. An example of this are registers (e.g. cancer registries), in which information is systematically collected and processed.

Analytical studies
Key findings of epidemiological research are based on analytical studies, e.g., casecontrol or cohort studies. The purpose of these studies is the testing of hypotheses. The transitions between descriptive and analytical studies are often smooth. The following study designs are also among the analytical studies.

- Longitudinal and cross-sectional studies
A cross-sectional study provides a snapshot of a particular group, in which one or more characteristics of study participants are recorded. A longitudinal study exists when the same group is interviewed for an extended period at different times. For example, epidemiological studies are cross-sectional studies, where the incidence or prevalence of a disease is examined at a given time, whereas the collection of data on immunisation after 1 week, after 2 months and after three years is considered a longitudinal study. Statements about causal relationships can be made only in longitudinal studies.

- Retrospective studies (looking back)
In retrospective studies, the relevant results have already been obtained and documented before the specific question of the study is formulated. The study data are usually collected from medical records or by questionnaires or interviews.

- Prospective studies (looking ahead)
In prospective studies possible influencing variables are determined before the final result of interest. As soon as the end result
has occurred, correlations between the influencing variables are analysed and the final result is analysed.

- **Observational studies**
  The investigator observes, documents and evaluates the data. Risk studies or prognosis studies are generally observational studies.

- **Experimental studies**
  In an experiment or an intervention study the investigator at least specifies the occurrence of the influencing variables. Experimental studies are usually analytical and prospective.

- **Single-centre study**
  Patients or volunteers are recruited from a single institution, such as a clinic.

- **Multicentre studies**
  Patients from multiple centres are summarised and analysed. This type of study is especially preferred for rare diseases or Phase III drug trials, so that a statistically sufficient number of participants can be recruited and thus the statistical power is increased.

### 6.5 Concepts in clinical research

Here are some key concepts and considerations that must be included in the study planning, implementation and evaluation of clinical studies.

**Logical considerations**

Before a research study plan is created, you should consider the following questions:
Is the study feasible under the given conditions? Are enough resources such as time, money, expertise and personnel available? Can the required number of patients be recruited within the scheduled time?

**Goal and influencing variables**
In the formulation of the problem and the derived hypotheses, the target variables to be measured (including dependent variables) and all relevant influencing variables (including independent variables, risk factors, predictors, factors, mediators, moderators) and their relationship to each other must be known.

**Ethics**
Not everything that is scientifically useful and feasible is also ethically justifiable. Therefore, all studies must be reviewed and approved by the responsible ethics committee based on applicable legislation and ethical principles.

**Patient information and consent form**
All study participants have the right to comprehensive information about the study. This is given in an objective and informative discussion and in the form of written patient information and a consent form. Before a patient participates in a trial, he must sign the consent form. With this he agrees to participate in the study, but has the right to terminate his study participation at any time without giving reasons and without prejudice for further treatment.

The consent form contains the following points (from www.swissethics.ch):
- General information about the study and the study objective
- Course, costs, type of examinations
- Voluntary nature of participation and right to withdraw
- Rights and duties of the study participant and the primary investigator
- Benefits and risks (including insurance) for the participants
• Data confidentiality
• Costs and compensation for the study participants
• Involuntary study termination
• Contact person

ICH GCP (Good Clinical Practice – International Conference on Harmonization)
The GCP has been a scientific and ethical standard regarding the planning, implementation, monitoring, data collection and analysis, and the reports of clinical trials in humans, since 1996. It serves to ensure data quality, the credibility of the study results and that the personal rights, security and data protection are guaranteed. The aim of the ICH is to harmonize the drug approval process in Europe, the USA and Japan. For more information on GPC-ICH, please visit www.ichgcp.net or www.ich.org.

Choice of a statistical model
Choosing a statistical model requires relevant professional skills (e.g., medical, biological, social, psychological or biomathematical knowledge). It is therefore even worthwhile to seek advice from a statistician in advance.

Specifics of data analysis
In the implementation of clinical or epidemiological studies, there are a number of peculiarities of data analysis.

• Clinical values and scales
Quantitative characteristics can be evaluated faster and more efficiently than qualitative ones. The result is the tendency to make quantitatively measurable matters that can actually only be described qualitatively. Through the introduction of clinical values and scales one can make complex traits or constructs (e.g., treatment success or quality of life) quantitatively measurable.
In contrast to the “hard” facts (such as surrogate markers) that can be measured exactly, these "soft" facts are actually estimates. For example, the Karnofsky Scale (with values from 0 to 100) is used to describe the general condition of a patient (symptom-related activity limitation, personal care and self-determination).

- **Outliers**
  The term outlier describes an extremely high or low value. Prior to analysis the data should be checked for outliers and the relevant study participants examined again if indicated.

- **Surrogate markers**
  The surrogate marker is a measured value whose change indicates the effect of an intervention (e.g., a new drug) on a super ordinate medical phenomenon (e.g., a tumour). The minimum requirement for a surrogate marker is the statistically significant relationship between it and the medical phenomenon. This includes, for example, in chronic myeloid leukaemia (CML), the molecular parameters such as Major Cytogenetic Response (MCyR), Complete Cytogenetic Response (CCyR) or Major Molecular Response (MMR).

- **Incorrect or incomplete information**
  When one is obtaining information, one is often dependent upon the statements of patients and relatives. However, they can intentionally (e.g., by deception) or unintentionally (e.g., due to loss of memory) make false or incomplete statements that can lead to misinterpretation of study results.

- **Censored data**
  In survival time studies the time until the occurrence of a particular event (e.g., until the death of a patient) is studied. However, the survival time can only be estimated for the following two reasons: For example, a patient can leave the study (a dropout) during the study because of unwillingness or for other reasons, or he
is no longer included in the analysis of survival time because he is still alive after the end of the study interval. The survival time in fact only provides information about the survival of a patient within a specified period of study, but says nothing about whether the patient continued to live after that. Data from patients that extend over the duration of a study and are therefore no longer included in the survival analysis are known as censored.

6.6 Phases of a drug trial from the first tests to approval (Stapff, 2004)

Before a new drug is approved by the authorities for the treatment of a disease, it must be tested in various phases for its efficacy and toxicity. A written consent for study participation is needed in all phases in which a drug is tested on humans. These phases are described briefly below.

Phase 0
Before a new drug is tested in humans, its toxicity must have been investigated in animal experiments, so that the drug is safe to be tested in humans.

Phase I
Phase I represents the first application in humans. This usually requires 10 to 15 healthy test subjects (exception: inclusion of patients with serious illnesses). The aim of this study is to demonstrate the tolerability of the drug. The investigations include analysis of the absorption, distribution, metabolism and excretion of the drug (pharmacokinetics and pharmacodynamics).

Phase II
Phase II includes the first clinical-therapeutic use of the drug on several hundred patients over a short period of time. The investigation of the therapeutic value and the pharmacological effect and
finding the right dose (minimum effective dose) and the necessary duration of treatment are the goals of these studies. Also of interest are interactions with other drugs, as well as the final dosage form (tablets, drops, capsules or others). Phase II and III trials are often placebo³-controlled studies that are conducted in a double-blind test⁴.

Phase III
In Phase III, the drug is tested in a large therapeutic trial of several thousand patients over a long period. The aim of these studies is the approval of the drug for commercial purposes. The focus of these studies is to further investigate the therapeutic benefits of the drug and to detect rare adverse events and unexpected findings. This phase may be conducted only after a positive implementation of Phase I and II. Once Phase III is completed, the manufacturer decides whether to apply for approval to the local authority to place the new product on the market.

Phase IV
Phase IV studies are conducted after approval of the drug. The aim is to accumulate further data on the efficacy and tolerability of the drug, e.g., by application observations. Here, under less strict and usually outpatient conditions, further information is obtained on the effects and side effects of the product.

¹ Placebo: Dummy medication without potential pharmacological effect.
² Double-blind trial: Both the study participants and investigators are unaware of whether the study participants are receiving the active ingredient or the placebo (study participants and investigators are "blind").
6.7 Approval authorities

Switzerland
Swiss Agency for Therapeutic Products (Swissmedic): Swissmedic is the approval and supervisory authority for medications. Every clinical trial must be reported to Swissmedic. Core competencies of Swissmedic include the approval and market surveillance of drugs, the operating license for manufacturing and wholesale trade and inspections, control of narcotics traffic, checking the quality of medicines and establishing legislation and regulations (www.swissmedic.ch)

Europe
European Medicines Agency (EMA): The EMA is responsible for the evaluation and supervision of medicinal products in Europe. Each drug must be approved through the centralized workflow. Six different committees (human and veterinary medicines, medicines for rare diseases, herbal medicinal products, paediatric medicines and novel therapies), consisting of patient and medical representatives of the EU and associated countries, evaluate the drug. The EMA constantly monitors the safety of drugs using a pharmacovigilance network. (www.ema.europa.eu)

America
Food and Drug Administration (FDA): The FDA is the official food inspection and drug administration authority of the United States of America. It is responsible for protecting public health by assuring the safety and effectiveness of human and veterinary drugs, vaccinations, medical equipment, food products, cosmetics, food supplements, other biological products and products that emit radiation. Drugs approved in the U.S. must have been manufactured by FDA-approved pharmaceutical manufacturers. (www.fda.gov)
Literature


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