# A review of the literature on the economics of noncompliance

## Room for methodological improvement

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**SUMMARY**

Therapeutic noncompliance is a major issue in health care, having important negative consequences for clinical outcome as well as for health care costs. This paper reviews the literature on the economics of medication noncompliance, identifies methodological shortcomings and formulates recommendations for future economic research in this area. Nine studies on the economics of noncompliance were assessed according to their definition and measurement of medication noncompliance, study design, and identification and valuation of costs and outcomes. Very diverse designs and often invalid methods for calculating costs were found. Medication noncompliance is often ill-defined and measured in an inaccurate way. The economic consequences of medication noncompliance have rarely been investigated according to the standard principles of good economic evaluation. No study could be retrieved that examined both costs and consequences of noncompliance in a cost-effectiveness analysis. Only two studies dealt with the cost savings from a specific compliance-enhancing intervention. There is a clear need for more and better research on the impact of noncompliance, on the cost-effectiveness of interventions and the potential of compliance-enhancing interventions to improve patient outcomes and/or reduce health care costs.

*Keywords*: compliance, economic evaluation, methodology

## INTRODUCTION

Therapeutic compliance can be defined as "the degree to which patient behaviour (in terms of taking medication, following diets, executing lifestyle changes, ...) is congruent with the recommendations of health care providers" [1]. For medication intake, compliance includes both regularity in dosing and timing of intake [2] and for some specific patient populations (e.g. HIV-AIDS patients) also food recommendations.

For the assessment of the economic consequences of noncompliance, costs and outcomes should be considered in a cost-effectiveness or cost-utility analysis. Cost-effectiveness and cost-utility analyses evaluate the "value for money" of health interventions and compare these across interventions to assist decision makers in health care in setting priorities between health interventions [3]. In cost-effectiveness analyses, outcomes are measured in well-defined physical units (e.g. live years saved), whereas in cost-utility analyses, outcomes reflect the subjective value of the results for the patients (e.g. quality adjusted life years or QALYs) [3].

Medication noncompliance entails costs due to the occurrence and consequent treatment of new or more morbid conditions and side-effects of medication. Under-dosing or extended time intervals between two intakes may increase morbidity, whereas over-dosing or shorter intervals between two intakes may increase unpleasant side-effects or toxicity of the medication. Moreover, buying medication without actually taking it, implies a pure economic production cost. In contract, if the untaken medication is not purchased, medication costs are decreased. The severity of the disease and the cost of the medication will determine whether these savings offset the treatment costs of increased morbidity.

As for the outcomes, medication noncompliance has often been associated with increased clinical risk in chronic patient populations, in terms of increased morbidity and mortality [4-10]. Less is known about the quality of life associated with medication noncompliance. If noncompliance would have an obvious negative impact on quality of life, and a positive impact on costs, there is no doubt that noncompliance is undesirable from the economic point of view. Unfortunately, the picture is not that clear, especially with regard to quality of life issues. There is conceptual obscurity in the precise relationship between quality of life and noncompliance. Noncompliance may improve patients' quality of life, for instance when they deliberately adapt their medication schedule to their own lifestyle, or it may decrease their quality of life due to increased moribidity and/or side-effects. However, poor or good quality of life may also be a trigger for noncompliance [11,12]. The effect of noncompliance on the cost-effectiveness of the treatment, if effects are expressed in terms of quality of life, then becomes ambiguous.

In practice, very few cost-effectiveness analyses correct for the factor of noncompliance [13,14]. The correction usually occurs in a sensitivity analysis, in which the impact of varying

compliance rates on the cost-effectiveness ratio of an intervention, is tested [14-15]. For example, Scharfstein et al. [14] found that the cost per QALY gained, of a specific prophylaxis regimen for Mycobacterium avium complex in patients with AIDS, was $25.000/QALY, using efficacy results from a clinical trial. The cost amounted to $34.000/QALY with an assumed noncompliance rate of 20%. In this particular case, the increase in the cost per QALY had no impact on the cost-effectiveness of the regimen relative to other prophylaxis regimens, but it could impact upon its cost-effectiveness relative to interventions in other patient groups. An example of a prophylactic regimen in which the relative efficiency was influenced by the assumed noncompliance rate, was provided by Jönsson et al. [15]. With a compliance rate of 70%, the use of prophylactic misoprostol in patients with osteoarthritis and nonsteroidal anti-inflammatory drug-associated abdominal pain was less costly than no prophylaxis. Because the regimen was also more effective in preventing gastric ulcers, it was obvious that misoprostol administration was a preferable option. However, with an assumed compliance rate of 60%, the regimen became more costly relative to doing nothing.

The assessment of the economic consequences of medication noncompliance is hampered by a number of methodological problems. These problems relate to the definition and measurement of noncompliance, the consideration of compliance-enhancing interventions and the appropriate design for the economic evaluation of noncompliance and the identification, measurement and valuation of noncompliance-related costs and outcomes.

## OBJECTIVE

The main objective of this study is to review the literature on the economics of noncompliance and explore the methodological problems in studying the economic consequences of noncompliance. Recommendations for future economic research in this area will be formulated.

## METHODS AND MATERIALS

A literature search was performed using Medline 1974-2000 and reference lists of retained articles. A combination of the following key-words was used: (non-)compliance, (non-) adherence, cost, economic, financial. Nine studies on the economics of noncompliance with therapeutic regimens were found. Four studied the costs of noncompliance in general, five the costs of medication noncompliance in specific diseases. No studies were found before 1990. This illustrates that the economic evaluation of noncompliance is a relatively young research area. Studies were excluded when noncompliance was not the main topic or when the economic

consequences of noncompliance were only peripherally addressed. Only original studies were included. Articles citing statements or general conclusions from other research groups without reference were excluded because it was impossible to assess the quality of the data and methods on which these conclusions were based. Studies about noncompliance with preventive health programmes were excluded after abstract review of the initial search results. Thus, nine studies were identified dealing with the economic consequences of noncompliance with therapeutic regimens.

A review table was created for the assessment of each article (tables 1 and 2). The subject of the study, noncompliance measurement methods, outcome and cost items included, methods for valuing the costs and the results of the study were recorded.

## RESULTS

In reviewing the literature on the economics of noncompliance, a number of problems were identified. The problems relate to the definition and measurement of medication noncompliance, consideration of determinants of noncompliance and compliance-enhancing interventions, study design, cost calculation and outcome measurement.

### Definition and measurement of medication noncompliance

In literature, a variety of operational definitions for (non)compliance are used. Whereas some definitions focus purely on medication noncompliance [16], other definitions use a composite construct in which not only medication noncompliance is assessed but also other therapeutic behaviour (e.g. following diet, executing lifestyle changes,...) [1]. The definition may encompass medication intake, regularity in dosing and timing of intake. In the economic literature on noncompliance, interruption or cessation of therapy is often used as a definition of noncompliance [17,18]. Sometimes, it is not specified what is understood by noncompliance [19]. Differences in operational definitions of noncompliance have implications for the techniques used to measure noncompliance or vice versa, which may, in turn, have great impact on the noncompliance rates found.

The studies in this review measured noncompliance by means of self-reports [20], collateral reports [21] or prescription refills [18] or used estimates on noncompliance rates from literature [17,19,22,23]. One article did not specify how noncompliance was assessed [24]. The absence of a "golden standard" for the measurement of noncompliance with medication regimens implies that a variety of methods is used in literature. Hence, comparison of noncompliance rates is often impossible.

Noncompliance may be assessed in relation to or in the absence of a clinical event [8,9]. For example, Col et al. [20] examined hospitalised elderly patients' history of noncompliance by means of self-report and found that 11,4% of the hospital admissions in elderly patients was due to noncompliance. Other examples of noncompliance assessment in relation to clinical outcome were provided by Iskedjian et al. [19], Coambs et al. [23] and Sullivan et al. [22] for medication noncompliance in general and Weiden et al. [17] for noncompliance with neuroleptic medication. Iskedjian et al. [19] and Sullivan et al. [22] both found a rate of 5,5% noncompliance-induced hospital admissions. Coambs et al. [23] estimated the rate between 6,5% and 10%, based on a literature review. In general, these noncompliance-rates are a reflection of the relative contribution of noncompliance in the aetiology of clinical events. This approach always underestimates the real rate of noncompliance, since not all noncompliant patients will experience adverse effects or increased morbidity. In contrast, as the effect of noncompliance may only become visible after a while, the association with noncompliance may not be made at the time of hospitalisation. If treatment costs are to be avoided, it is important to identify noncompliant patients before the negative event has taken place, i.e. subclinical noncompliance [8]. In the literature on the economics of noncompliance, only two studies used this approach [18,25]. McCombs et al. [18] assessed subclinical noncompliance by means of prescription paid claims data and evaluated hospital admissions, ambulatory care, prescription drugs and use of skilled nursing home services in patients that interrupted or continued therapy in the first year after initiation of the therapy. Swanson et al. [25] measured noncompliance in renal transplant patients by means of an interview. Clinical events in compliant and noncompliant patients were evaluated and hospital admissions recorded to study the impact of noncompliance on hospitalisation costs. Apart from these two exceptions, the cost reported in most studies is likely to be an underestimation of the real cost attributable to noncompliance, due to sub-optimal noncompliance measurement.

**Compliance-enhancing interventions**

Although a number of studies pointed at the cost consequences of noncompliance, only two studies measured the cost consequences of a compliance-enhancing intervention [21,24]. Levenson et al. [24] performed a descriptive study in eight noncompliant patients with potentially fatal asthma. The intervention consisted of patient education, regular clinic visits with the same physician, simplified medical regimens, psychiatric interventions if necessary, and adequate doses of anti-inflammatory medications. The intervention was based on a literature review of the determinants of noncompliance in patients with severe asthma. The annual mean charges per patient were found to decrease from $22999 (s.d. $20639) before the intervention to $1107 (s.d. $1618) after the intervention. The cost of the intervention was not assessed. Despite the limited sample size and the descriptive nature of the study, the results give an indication of the

potential cost-reducing effect of compliance interventions. Weis et al. [21] examined the cost impact of directly observed therapy (DOT) to improve medication compliance in tuberculosis patients relative to traditional therapy. Whereas in traditional therapy (N = 257) medications are self-administered by the patients, universal DOT (N = 402) is a program in which health care personnel witness all patients taking all prescribed medications. The latter may require health care personnel to travel to places agreed upon with patients for the administration of the medication. Although seemingly very resource intensive, DOT was found to be less expensive than traditional therapy for both in-patient and out-patient health care due to the avoidance of noncompliance-induced extensions of therapy duration, relapses and acquired resistance. The savings from shorter therapy times and reduction of relapses and acquired resistance more than offset the additional manpower and transportation costs incurred with DOT. The cost of in-patient care was $24710 per patient per therapy for traditional therapy and $9040 for DOT; the cost of out-patient care was $2920 for traditional and $2220 for directly observed therapy. This study clearly illustrates the potential of compliance-enhancing interventions to decrease health care costs, although it might not be feasible to generalise DOT to all patient groups.

**Study design**

Most studies use a simple multiplicative model to estimate the costs associated with noncompliance. Cost estimates are obtained by multiplying noncompliance rates, derived from literature or direct observations, with national annual hospitalisation cost estimates [17,19,22], annual mean hospital charges per patient [24], Medicaid paid claims data [18], annual hospital and nursing home expenditures [23] and average ambulatory care expenditures [23]. For example, Sullivan et al. [22] estimated costs by multiplying the noncompliance-induced hospitalisation rate found in literature with the national annual cost estimate for all hospitalisations in more than 6,430 U.S. hospitals.

One study used an inferential approach to draw general conclusions about the likely effect of noncompliance on costs, without actually trying to provide cost figures [26]. The inferential approach makes use of the transitivity principle of relationships to establish a relationship that has not been examined in literature. The authors reviewed the literature and found a relationship between noncompliance and certain psychosocial factors (e.g. depression, stress, social support and personality disorders), which were, in turn, related to health care utilisation (Figure 1). From both relationships, a third relationship between patients characteristics and health care utilisation was inferred. Basically, it turned out that on the one hand noncompliance was associated with more depression, less social support, more stress and the presence of personality disorders. On the other hand, depression, lack of social support, stress and personality disorders were

associated with increased health care utilisation. Hence, it may be assumed that noncompliant patients are likely to have higher health care utilisation [26].

FIG. 1

**Costs**

Apart from a few exceptions [18,21,22,23], most of the reviewed studies are fairly limited to hospitalisation costs [17,19,20,24,25]. The calculation of hospital costs was done either by multiplying the number of hospitalisation days due to noncompliance with the per diem price [17-19,22,24] or by multiplying rates of noncompliance, as found in literature, with aggregate cost figures for all health care services in a given country [23]. Reported annual hospitalisation costs of medication noncompliance in general varied from CAD$0,6 billion in 1998 in Ontario, Canada [19] to $8,5 billion in the U.S. in 1986 [22]. This represents 0,8% and 1,7% of all health care expenditures in these respective countries. For specific diseases, it was estimated that in renal transplant patients $9000 hospital costs per patient per year could be saved if patients would be compliant [25]; in hypertensive patients, Medicaid California could save $636,9 in the first year if patients did not discontinue their therapy; in tuberculosis patients, medication noncompliance was found to account for an additional cost of $19460 per patient per therapy for hospital care and $1637 per patient per therapy for ambulatory care [21]. As for productivity costs and costs of premature death due to medication noncompliance in general, Sullivan et al. [22] provided an estimate of twice the direct costs, i.e. $17 billion per year, whereas Coambs et al. [23] valued these costs as once the direct costs ($3,53 billion). Nursing home costs and ambulatory care costs were valued at $0,66 billion and $1,09 billion respectively [23], using national nursing home expenditures and average expenditure per physician visit. The study by Weis et al. [21] used activity reports to calculate the real resource use of health care personnel for a compliance-enhancing intervention. Service time as well as travel time were carefully recorded. Thereafter, time units were multiplied by hourly wage rates to obtain the cost of personnel attributable to the intervention. Travel mileage, number of laboratory tests, number of X-rays and medication doses prescribed were used in combination with unit market prices to calculate the costs of the respective items. Some authors did not specify their methodology for measuring and valuing hospitalisation and/or other costs [20,25].

**Outcome**

A full economic evaluation of noncompliance requires, in principle, the inclusion of a single outcome measure, either in clinical terms such as survival, or in terms of quality of life. None of the reviewed articles included an outcome measure in its analyses.

## RECOMMENDATIONS

It is clear from the above review that the study on the economics of medication noncompliance lacks methodological rigour. Box 1 lists a number of criteria according to which economic evaluations of noncompliance can be assessed.

BOX 1

### Definition and measurement of noncompliance

Defining, and even more, measuring noncompliance is a difficult and daunting task. Different definitions and measurement methods with different degrees of accuracy have been used in literature. Medication noncompliance can be measured my means of observation, biochemical assays, markers, self-report, collateral reports, pill-counts, prescription refills and electronic event monitoring (EEM). Self-reports, collateral reports, pill-counts, prescription refills and assays usually underestimate the real rate of noncompliance and do not provide insight into the dynamics of noncompliance [9]. EEM is a technologically advanced and reliable method to assess medication noncompliance, consisting of a pill bottle, fitted with a cap, which contains an electronic circuit, registering the date and time of openings and closings of the bottle. Although there is no certainty about the actual intake of the medication, EEM has been shown to have superior sensitivity compared to other methods [7]. Moreover, EEM data provide insight into the dynamics and pattern of the medication intake [9]. The technique is relatively expensive, however, and requires co-operation from the patient.

The suitability of an instrument to measure noncompliance depends on the medical treatment under consideration and the objective of the compliance measurement. Markers, for example, are substances that are co-formulated with the drug under study. It is not feasible to use markers for noncompliance measurement beyond clinical trials. Biochemical analysis of blood, urine or other bodily secretions is only applicable to medications with a long half-life and does not preclude "white coat compliance", i.e. patients taking their medications correctly close to a pending visit [9]. Nevertheless, these instruments may be useful complements of EEM [27] or in situations where the medication intake cannot be monitored with EEM. Observation, for instance, is valuable when complex behaviours must be performed (e.g. metered dose inhaler use in asthma patients) but does not allow compliance monitoring beyond the clinical environment. Self-reports may be useful if limited resources are available for compliance monitoring, as it is a cheap and simple instrument. Prerequisite is that the questions are posed in a non-threatening, non-accusatory and open-ended way [8-10]. The choice between compliance measurement

instrument should be guided by the focus on subclinical noncompliance if noncompliance-induced costs are to be avoided.

For the analysis of noncompliance data, it is important to be aware of the different degrees and different types of medication noncompliance [27]. The impact of noncompliance on, as well as the relevant levels of noncompliance for, health care costs will be variable across diseases. Patients may be highly or moderately noncompliant, be noncompliant with dosing, timing or intake and be noncompliant with a more or less 'forgiving' treatment [2]. Forgiveness refers to the extent to which the therapeutic effect of a drug is lossed if treatment is not followed as prescribed (e.g. if doses are missed, timing is not respected,...). Noncompliance with immunosuppressive therapy after transplantation, for instance, is likely to be less forgiving than noncompliance with antimycotic pharmacotherapy (i.e. terbinafinum) for mould of a toenail, as the risk for mobidity and mortality due to noncompliance has already been substantiated in transplant patients. The pharmacologic features of the medication also play a major role in the impact of noncompliance. Resuming medication intake after a drug holiday, for instance, may either result in "recurrent first-dose effects" or a rebound effect in the drug-regulated variable [28]. A first-dose effect refers to the toxic effect of some drugs if treatment is started. Smaller doses are therefore given at the beginning of the therapy to avoid these effects and dosages are increased once the counter-regulatory mechanisms are initiated. However, drug holidays followed by resumption of medication therapy initiates recurrent first-dose toxicity [28]. A rebound effect may occur if the counter-regulatory mechanism fades more slowly than the pharmacologic action, as is the case, for example, with non-ISA beta blockers [28,29].

**Compliance-enhancing interventions**

Literature on the cost-effectiveness of compliance-enhancing interventions is relatively limited [1,27]. The cost-effectiveness of a compliance-enhancing intervention will depend upon the costs and health effects associated with the usual care and the intervention's own costs and health effects.

To date, the evidence on the appropriate design of compliance-enhancing interventions is limited [30]. The identification of modifiable determinants and characteristics associated with noncompliance is an important but difficult first step in the development process of an intervention programme [27]. Evidence on the determinants of noncompliance is growing [8,31-33] but often lacks methodological strength in measuring noncompliance. Most compliance-enhancing interventions are complex, consisting of combinations of providing information, counselling, patient education, reminders, less complex treatment regimens, and other forms of increased supervision [30]. Only few interventions tested in randomized clinical trials have shown improvements in compliance, and even fewer in clinical outcome [30]. As the trial period

is often rather short, long-term benefits of compliance-enhancing interventions can rarely be shown.

For the analysis of the cost-effectiveness of compliance-enhancing interventions, it is important to look at both costs of the intervention and outcomes, not only in terms of compliance, but also in terms of subjective value of the clinical outcome for the patient. If the intervention offers better outcome than usual care and if its cost is more than offset by the cost-savings from reduced noncompliance, the intervention is worthwhile. However, even if the intervention implies a slight increase in costs, society may still opt for this intervention if, for instance, increasing compliance improves patients' outcome. Society's willingness to pay for the additional benefit then determines the acceptance of the intervention.

**Study design**

The most straightforward design for studying the economics of noncompliance is direct observation. In this approach, both cost and compliance data are based on individual patient records or direct observations. It is obvious that this is a very resource demanding approach but allows detailed measurement of real resource use and avoidance of bad proxies for costs like per diem hospital charges.

If direct observations on compliance, costs and outcomes are not feasible, data from existing sources may be modelled. A simple example of a decision model applied to noncompliance is shown in Figure 2. Following treatment, a patient is compliant or noncompliant, depending on a complex interaction of internal and external factors [27]. Noncompliant patients have a chance p to get complications (increased morbidity), whereas compliant patients have a chance q to get complications (side-effects of medication), where $q < p$ [4,5,8,10]. Different types of complications may be considered (with different probabilities of occurrence), which only enlarges the decision tree but does not change the basic idea. Probabilities p and q may come from epidemiologic data (prevalence rates), clinical trials, literature or, less accurate, expert opinion.

FIG. 2

Expected treatment costs for compliant and noncompliant patients are obtained by summing the costs of treating complications, weighted by their probability of occurrence [3]. The effect of varying one or more assumptions (e.g. the probability of getting a complication) should be tested in a sensitivity analysis [34]. The prerequisite for the model to give reliable results is that the cost data of complication treatments are obtained in accordance with the standard principles of

cost calculation (cf. section on costs). This requires special attention when using cost data from the literature.

The problem with the use of models to study the economic consequences of noncompliance is that minimal data have to be available (e.g. the risk for complications, the cost of treating these complications,...). In the case of noncompliance, insufficient or only inaccurate data are often present. Additional data collection may therefore be needed.

**Costs**

Most studies in the review used data on national hospital expenditures, per diem costs combined with average length of stay or charges to calculate the cost of noncompliance.

Per diem costs, charges or reimbursement data are, however, no good representation of real economic hospital costs because they do not reflect the real value of the resources used during a process [3].

The limitation to hospital costs in most studies is troublesome. Hospital cost data are of limited use for health care policy, since they do not reflect real societal costs associated with noncompliance. Health care costs associated with the treatment of noncompliance-related complications include, besides hospitalisation costs, also ambulatory care costs, laboratory tests, medical supplies, etc. [3,22,23]. Moreover, noncompliance induces non-health care costs: production losses, travel expenses, time costs of relatives, ... [3,22,23]. Resource use in other sectors may be affected by noncompliance as well if, for instance, patients need child care during their hospitalisation or have to hire a housekeeper [3]. The best approach to value real resource use is to measure every single cost item in detail and value it according to its market price [35]. Although very resource intensive, this approach offers the most valid cost data.

The differences in relevant costs from the different perspectives emphasises the importance to explicitly state the point of view from which the cost calculation is performed. A hospital considering the introduction of a compliance intervention, for instance, will be interested in the cost of noncompliance to the hospital itself, whereas a health policy maker will be more interested in the cost of noncompliance from the societal point of view, when considering financial support for compliance interventions. It is always useful to use a broad cost concept in the analysis, that is, to include both health care costs and non-health care costs. Transparency in the data report gives the reader the opportunity to derive results that are relevant for his own setting and purpose.

Given the lack of evidence about the real rate of noncompliance in different diseases, the absence of a "general" noncompliance rate and the impossibility to measure and value real resource use in all patient groups, it is not very useful to examine the cost of noncompliance "in

general". Results would only be obtained under a multitude of assumptions, such that, in a sensitivity analysis, the range of possible outcomes becomes so large that it is impossible to draw firm conclusions from the data.

**Outcome**

A major shortcoming in current literature on the economic consequences of noncompliance is the eminent absence of an appropriate outcome measure. It is often stated that the quality of a cost-effectiveness analysis depends on the quality of the effectiveness data it uses [3]. In this respect, it is important to be cautious with using results from randomised clinical trials. In clinical trials, conditions are usually highly controlled and stringent follow-up protocols preclude noncompliance. Therefore, the results will not reflect expected results in real life situations. The results reflect efficacy rather than effectiveness of a medication and therefore need to be adjusted for noncompliance before they can be used in economic evaluations [36,37]. If compliance with the trial medication would not be closely monitored in Phase III randomised clinical trials, the outcomes of the trial would result in erroneous dosing recommendations [2]. Noncompliant patients would dilute actual treatment effects in a way that makes the investigator erroneously conclude that higher dosages are needed to obtain the desired outcome. As a consequence, compliant patients will be exposed to higher drug levels that potentially lead to unwanted side-effects [2], sometimes requiring additional (expensive) treatment.

Although evidence is growing that noncompliance with effective medication regimens is associated with worse clinical outcomes, the *perceived* outcome by the patient may be different. Given that noncompliant patients may experience clinical consequences that are very different from those experienced by compliant patients (e.g. compliant patients may suffer more from a drug's side-effects whereas noncompliant patients may suffer more from recurrence or worsening of their original disease) and given that different outcomes may be important for compliant and noncompliant patients, quality of life is the most appropriate outcome measure in economic evaluations of noncompliance. However, a note of caution is appropriate. The introduction of quality of life in the cost-effectiveness picture entails a possible conceptual leap. On the one hand, quality of life may be seen as an outcome of noncompliance [38,39], on the other hand, it may be considered a trigger for noncompliance [11,12]. The causal relationship between both concepts cannot be examined in an experimental design due to ethical objections. Patients cannot be forced to be noncompliant with their medication regimen if the efficacy of this regimen is proven. Causality could only be assumed if compliance-enhancing interventions would prove to have an impact on both compliance and quality of life.

Studies in different disease areas have shown that noncompliance may either be not [40], positively [12] or negatively [41] related to quality of life, indicating that it makes no sense to try

to draw general conclusions about the relationship between compliance and quality of life. The quality of life consequences of noncompliance need to be reviewed for every medical regimen, as different medications have different characteristics and hence different consequences [28].

To be useful for economic evaluation, quality of life of compliant and noncompliant patients should be measured as an index. Clinical studies about the quality of life consequences of noncompliance commonly use disease specific quality of life profile measures [42,43]. Quality of life profiles are useful as complementary information but are, as such, not useful in economic evaluations because they most often cannot easily be transformed into one single index. Therefore, a generic instrument leading directly to a quality of life index will be used in economic evaluations [3]. Examples of such instruments are the EuroQol [44], the Health Utilities Index [45,46] and the Quality of Well-Being Scale [47].

**Cost-effectiveness**

Although the literature review was focused on studies about the economic consequences of noncompliance, only cost calculations were found. To get a full picture of the economic impact of noncompliance, the costs and effects associated with noncompliant behaviour should be compared to the costs and effects of compliant behaviour in a cost-effectiveness analysis.

From the reviewed literature, it can be concluded that treating noncompliant patients is likely to be more costly than treating compliant patients but the outcome of noncompliance, in terms of quality of life, is uncertain. Two scenarios are graphically represented in Figure 3. The horizontal axis represents the difference between the costs with and without the intervention and the vertical axis the difference between the quality of life with and without the intervention. Dot C represents the cost-effectiveness of an intervention if all patients are compliant. The intervention improves the patients' quality of life at a certain cost. All states to the north-west of C (quadrant I) are more cost-effective than state C, all states to the south-east (quadrant IV) are less cost-effective. NC1 (costs and effects of the intervention for noncompliant patients) represents the intuitive state in which noncompliant behaviour is more expensive and offers worse quality of life than compliance. The average cost-effectiveness of the intervention (A1) for the entire patient group decreases due to noncompliance. In this case, compliance-enhancing interventions could increase the average efficiency of the treatment by moving A1 closer to C.

NC2 represents a situation in which noncompliant patients have a better quality of life than compliant patients, be it at a higher cost. Patients' adaptation of their medication schedule to their own lifestyle may, despite their higher treatment costs due to new of more morbidities, lead to a better quality of life. Whether the average cost-effectiveness (A2) for the entire patient group is then acceptable depends on the society's willingness to accept the additional cost for the additional benefit. As long as the society is not willing to pay for the additional benefit, it is

worth considering compliance-enhancing interventions to increase the treatment's cost-effectiveness.

FIG. 3

## CONCLUSION

Therapeutic noncompliance is a behaviour that leads to increased health care costs and decreased cost-effectiveness of interventions. For both clinicians, policy makers in health care and the patient, it is important to take the impact of noncompliance on the cost-effectiveness of interventions into account. Studies about the economic consequences of noncompliance are generally performed in a very elementary way. Costs are not valued according to the standard principles of cost calculation and outcomes, in terms of quality of life, are never related to costs in a cost-effectiveness ratio. It is important, however, to correct cost-effectiveness data for the impact of noncompliance

Whether or not compliance interventions are worthwhile, can only be presumed after careful consideration of both costs and outcomes of noncompliance. A lot of work remains to be done in testing the cost-effectiveness of compliance interventions and the impact of noncompliance on the cost-effectiveness of health interventions. The methodological considerations of good economic evaluation as well as the methodological issues of measuring noncompliance should be taken into account in performing these analyses.

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**Table 1: Studies on the cost of medication noncompliance in general**

| Author | Subject | Noncompliance measurement | Cost items included | Method for valuing costs | Results |
|---|---|---|---|---|---|
| Col e.a.1990 [20] | drug-related hospital admissions in elderly patients | - self-report | - hospital costs | - not specified | - total cost of 36 hospital admissions related to NC: $77.289 |
| Sullivan e.a. 1990 [22] | medication NC (U.S.) | - literature | - hospital expenditures | - ALOS[1] × per diem cost | - $8,5 billion per year |
| | | | - lost productivity and premature deaths | - 2 × direct cost | - $17-$25 billion per year<br>**Total $25,5 – $33,5 billion per year** |
| Coambs e.a. 1995 [23] | Medication NC (Canada) | - literature | - hospital expenditures | - rate of NC-related admissions × total hospital expenditures | - $1,78 - $2,72 billion |
| | | | - nursing home expenditures | - rate of NC-related nursing home admissions × total nursing home expenditures | - $0,66 billion |
| | | | - ambulatory care costs | - rate of NC-related physician visits x total number of visits × average expenditure per visit | - $1,09 billion |
| | | | - productivity and mortality costs | - 1× direct costs | - $3,53 - $4,49 billion<br>**Total $3,53 - $4,49 billion per year** |
| Iskedjian e.a. 1998 [19] | Medication NC (Ontario, Canada) | - literature | - hospital expenditures | - ALOS[1] × per diem cost | - $633 million per year in a population of 11 million. |

[1] ALOS = average length of stay

**Table 2: Studies on the cost of medication noncompliance in specific diseases**

| Author | Subject | Noncompliance measurement | Cost items included | Method for valuing costs | Results |
|---|---|---|---|---|---|
| Swanson e.a. 1992 [25] | Renal transplantation | - self-report | - hospital costs | - not specified | Over a period of 3 years, 9 months:<br>- cost compl. patient: $28541<br>- cost NC patient: $12885<br>- cost of NC: $900/patient/year |
| McCombs e.a. 1994 [18] | Hypertension | - paid claims data for prescription refills | - hospital costs<br>- nursing home care costs<br>- ambulatory care costs<br>- prescription drug costs<br>- long term care costs | - LOS[1] × average per diem cost to Medi-Cal[2]<br>- LOS × average per diem cost to Medi-Cal<br>- actual Medi-Cal payments<br>- actual Medi-Cal payments<br>- actual Medi-Cal payments | - reduction of $636,9 in 1st year<br>- included in hospital costs (?)<br>- reduction of $174,55 in 1st year<br>- increase of $281,34 in 1st year<br>- reduction of $61,34 in 1st year<br>**Total reduction: $591,46 in 1st year** |
| Weiden e.a. 1995 [17] | Schizophrenia | - literature | - hospital costs | - re-hospitalisation cost = ALOS[3] × per diem cost × number of relapses (survival analyses)<br>- excluding capital, medication or doctor services costs. | national cost of re-admissions due to NC:<br>1st year: $370 million<br>2nd year: $335 million<br>**Total cost in two years: $705 million** |
| Levenson e.a. 1997 [24] | Asthma – noncompliance intervention | - not specified | - hospital costs | - hospital charges | - before intervention: mean cost per person per year $22999 ± $20639<br>- after intervention: mean cost per person per year $1107 ± $1618 |
| Weis e.a. 1999 [21] | Tuberculosis – compliance intervention | - collateral report physician | - hospital costs<br>- ambulatory care costs<br>- personnel<br>- travel time<br>- laboratory tests<br>- X-rays<br>- medication | - LOS × billing rate per diem<br>- service + travel time × hourly wage<br>- health department reimbursement rate per mile × mileage<br>- market price per test × number of tests<br>- market price × number of X-rays<br>- market price × dose | - Hospital care:<br>Tradit. therapy: $24710 per patient<br>DOT[4]: $9040 per patient<br>- Ambulatory care:<br>Traditional therapy: $2920<br>DOT: $24710 per patient |

[1] LOS = Length of Stay
[2] Medi-Cal = California Medicaid

[3] ALOS = Average Length of Stay
[4] DOT = Directly Observed Therapy

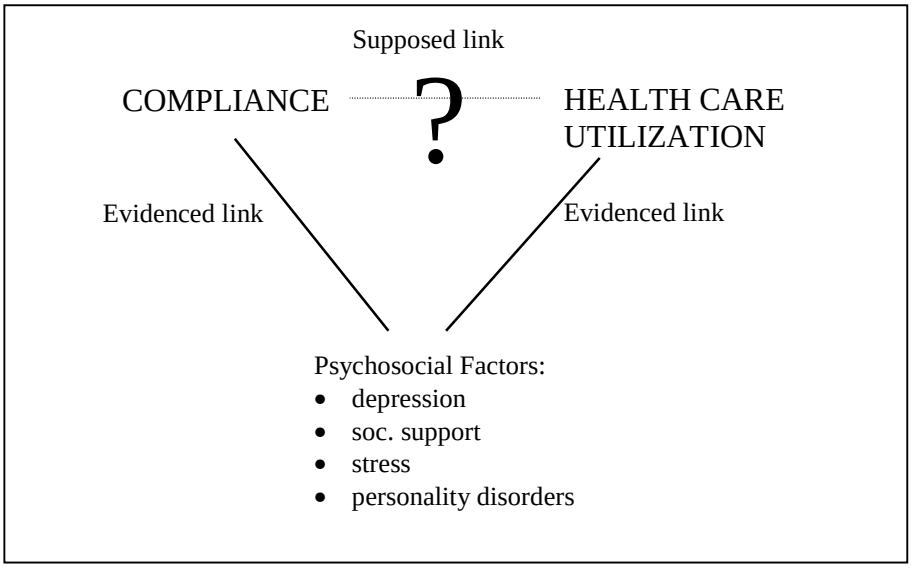


**Figure 1: Indirect inference from psychosocial and economic evidence**

*Irina Cleemput et al.*

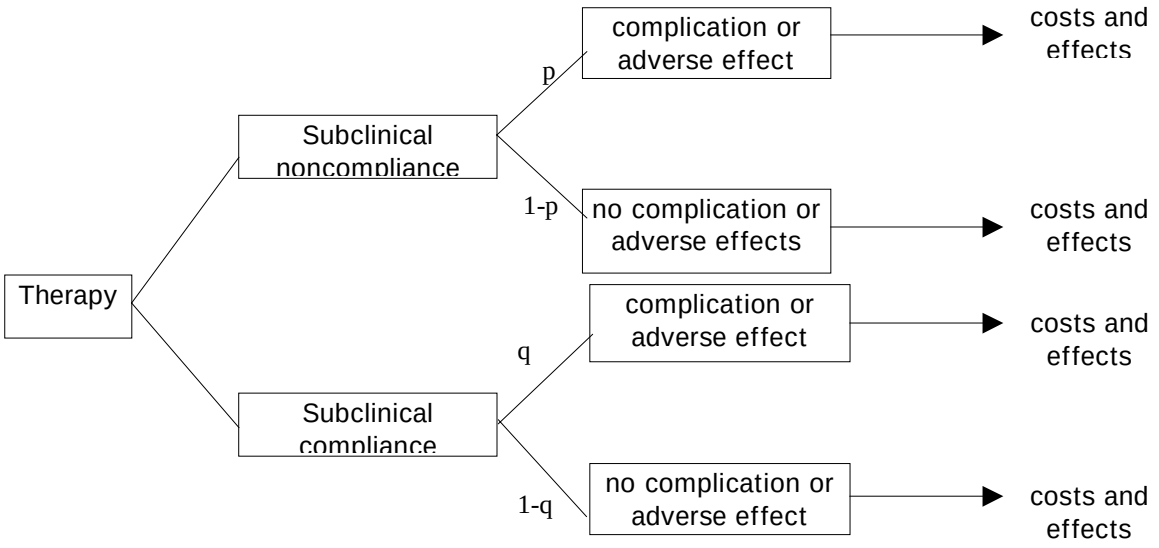


**Figure 2: Decision tree for noncompliance**

*Irina Cleemput et al.*

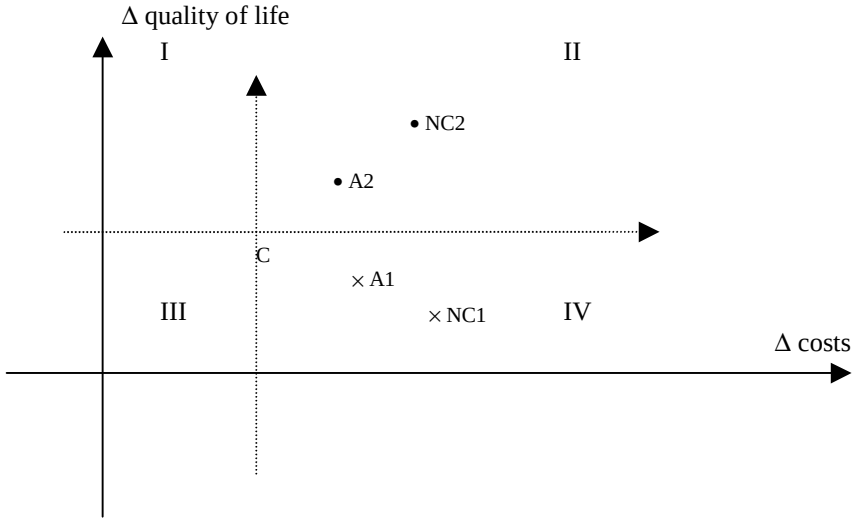


**Figure 3: Cost-effectiveness in compliant versus noncompliant patients**
(adapted from Drummond et al. (1997))

**Definition and measurement of noncompliance**

1. Was noncompliance defined in an explicit and unambiguous way?
2. Was noncompliance measured according to the best available standards? What are the potential biases in the results?

**Study design**

3. Did the study involve a comparison between compliant and noncompliant patients?
4. Was the viewpoint for the analysis stated?
5. Was allowance made for uncertainty in the estimates of costs and consequences? Was a sensitivity analysis performed?

**Costs and outcomes**

6. Did the study examine both costs and consequences of noncompliance?
7. Were all relevant costs and consequences of noncompliance identified? Were costs beyond hospital costs considered? Was quality of life included as an outcome measure?
8. Were costs and consequences measured accurately and valued in appropriate units? If secondary data were used, was the accuracy of the data established?

**Cost-effectiveness**

9. Was an incremental analysis of costs and consequences of noncompliance performed?

**Discussion and conclusion**

10. Were study results sensitive to changes in values?
11. Did the presentatien and discussion of study results include all ussues of concern to users?

**Box 1: Checklist for assessing the economic consequences of noncompliance**

(Adapted from Drummond et al. [3])