Pharmaceutical Care of Adolescents with Type 1 Diabetes Mellitus:

DIADEMA Trial: A Randomized Controlled Trial

INAUGURAL-DISSERTATION

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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IV. List of Abbreviations

ADA	American Diabetes Association
AEs	Adverse events
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CRFs	Case report forms
CSII	Continuous subcutaneous insulin infusion
DAWN study	Diabetes Attitudes, Wishes and Needs study
DCCT	Diabetes Control and Complication Trial
DDG	German Diabetes Society (Deutsche Diabetische Gesellschaft)
DIADEMA study	Diabetes in Adolescence Engagement and Monitoring in phArmacies study
DKA	Diabetic ketoacidosis
DRPs	Drug-related problems
EDIC study	Epidemiology of Diabetes Interventions and Complications study
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
ICT	Intensified conventional therapy
ICH	International Conference on Harmonization
IU	International units
ISPAD	International Society of Pediatric Diabetes
LDL	Low density lipoprotein
PCP	Pharmaceutical care plan
PhC	Pharmaceutical care
SAEs	Serious adverese events
SMBG	Self-monitoring of blood glucose
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

WHO	World Health Organization

V. Summary

This thesis examines a new approach in the care of adolescents with type 1 diabetes mellitus (T1DM), by extending the provider outreach and including pharmacists into the multidisciplinary care of such adolescents. The impact of pharmaceutical care on clinical outcomes and its limitations were explored in our DIADEMA (DIabetes in ADolescence Engagement and Monitoring in phArmacies) study, conducted in two countries, Bosnia-Herzegovina and Germany. The study and its results are presented and evaluated as the main focus of this thesis.

In section 1, the necessity for such a study is explored, as the incidence of T1DM is increasing worldwide. Despite modern therapies, adolescents with T1DM often have low adherence to complex insulin regimens, leading to poor glycemic control. Over time, this lack of glycemic control can lead to micro- and macrovascular complications, increased morbidity, and premature mortality. The treatment of complications of T1DM represents a major economic burden.

The concept of pharmaceutical care is also presented in section 1, and the benefit of pharmaceutical care is explored in adults with type 2 diabetes mellitus (T2DM). However, evidence in adolescents with T1DM remains scarce, which was an additional motive for conducting the DIADEMA study. The main objective of the study is to evaluate the impact of pharmaceutical care in adolescents with T1DM by a multidisciplinary team on multiple important clinical outcomes. The study was carried out in two sites, one each in Germany and Bosnia-Herzegovina.

In section 2, the objectives and the main outcome measures of the DIADEMA study are presented. These measures include the change from baseline in glycated hemoglobin (HbA1c), the number of severe and non-severe hypoglycemic events, patient wellbeing, and satisfaction with pharmaceutical care, drug-related problems, and adherence with treatment guidelines.

Section 3 presents the methods of this randomized, controlled, prospective, multicenter study. A total of 68 adolescents with T1DM were included. The intervention group received monthly structured pharmaceutical care delivered by pharmacists plus

supplementary phone calls, for 6 months. The control group received usual diabetic care. Data were collected at baseline and after 3 and 6 months.

The results of the study are presented in section 4. A significantly greater improvement in HbA1c was observed in the intervention group than in the control group after 6 months (change from baseline −0.54 vs. +0.32%, p = 0.0075), even after adjustment for country-specific variables (p = 0.0078). However, the effect was more pronounced after only 3 months (−1.09 vs. +0.23%, p = 0.00002). There was no significant difference between the two groups in the number of severe hypoglycemia events. At 3 and 6 months, the intervention group did not have a significant change from baseline in the frequency of non-severe hypoglycemic events, but had a significant improvement in wellbeing. Patients were highly satisfied with the pharmaceutical care intervention.

The conclusion of the study is that the improved outcomes provide new evidence that pharmaceutical care adds value in the management of T1DM in adolescents.

In section 5, the positive aspects of the study such as improved HbA1c outcome, enhanced wellbeing and satisfaction as a result of pharmaceutical care are highlighted and discussed, as well as the problem of decreased motivation in adolescents intrinsic to their developmental stage, emphasizing the need for further research of the optimal methods to achieve sustained long-term improvements in this specific patient population.

VI. Motivation, Rationale, and Aim of the Thesis

In children and adolescents, T1DM is the most common endocrine disorder. Epidemiological studies show an alarming rise in the worldwide incidence of T1DM; small children in particular are increasingly affected. In addition, T1DM is the leading cause of nephropathy, retinopathy, and neuropathy, as well as a major cause of cardiovascular disease and premature mortality. Only near-normal glycemic control can effectively reduce the rate of diabetes complications. More than ever, the everyday management of T1DM poses a significant burden on the affected patients and their families.

According to German estimates, around 30,000 children and young people aged under 20 years have T1DM, with approximately 2,500 new onset patients every year. The disease can manifest at any age and is associated with an increasing incidence in recent years. In the last 10 years alone, the number of new cases has doubled. Consequently, healthcare resources in many countries are insufficient to cope with the growing demand. T1DM in children and adolescents requires intensive supervision and monitoring to prevent acute and late diabetes complications and to improve quality of life.

Adolescents with T1DM may develop late diabetes complications in adulthood, such as diabetic retinopathy with a risk of blindness, diabetic nephropathy with a risk of renal failure, and diabetic neuropathy with a risk of diabetic foot ulcers. Young patients are often non-adherent to insulin and exercise recommendations, as they do not respect or implement drug therapy properly. Chronic suboptimal glycemic control will eventually result in diabetes complications; indeed, despite modern therapies, more than 50% of all young people with diabetes will develop at least one late complication. Over time, inadequate glycemic control inevitably results in diabetic micro- and macrovascular complications. The costs of treating acute and late diabetes complications are significant and represent a major burden on healthcare systems.

This problem exists in many countries, including Bosnia-Herzegovina and Germany. A study in the USA by Patino et al. (2005) found that young people do not adhere to the

insulin and nutrition recommendations, with 75% not controlling their blood glucose levels appropriately, and 64% not adhering to physical activity recommendations.

In addition to making regular visits to the children's hospital, community-based pharmacists distribute insulin to young people with T1DM. Pharmacists are the most accessible healthcare professionals. These were leading foundations in the design of this project, to evaluate that pharmacists could provide pharmaceutical care, competent advice, and support to the youth with T1DM during the course of their disease.

The underlying questions of this thesis were to explore if the integration of pharmacists into diabetes teams can improve existing care structures and help to reduce the rate of preventable acute and late complications. An initial leading thought and additional long-term question (that is beyond the scope of this 6-month study) was whether an integrated care and multidisciplinary approach can reduce health-related costs, such as the cost of medication and hospitalization due to acute and late complications.

We believed that in less developed countries, such as Bosnia-Herzegovina, where there is an acute shortage of healthcare and other resources, pharmacists could contribute greatly to the care of adolescents with T1DM.

Another aim of this project was to define a practical binational pharmaceutical care support program for adolescents with T1DM for community-based pharmacists, which could results in better adherence to therapy and to international treatment guidelines. Studies in adults with diabetes mellitus or coronary heart disease have shown that the involvement of pharmacists in a multidisciplinary care team led to better patient outcomes (Wermeille et al. 2004, Chisholm-Burns et al. 2010, Neto et al. 2011).

The present study aims to evaluate the impact of intensified pharmaceutical care, based on pediatric diabetes guidelines, on clinical outcomes in adolescents with T1DM. The clinical outcomes include Hb1Ac (without an increase in hypoglycemia) and patient wellbeing, and may contribute to the prevention of acute and late diabetes complications.

Last but not least, my very good friend, who was born in 1977 in Bosnia-Herzegovina, was diagnosed with T1DM at the age of 3 years. During adolescence diabetic

neuropathy evolved, accompanied later by evident glycemic variability and blood pressure problems. At the age of 25 she developed diabetic retinopathy which progressed and resulted in few years in total blindness. Therefore, it is my personal motivation to draw attention to the problems that adolescents with T1DM face, and to the prevention of acute and late diabetic complications.

1. Introduction

1.1. Pediatric Type 1 Diabetes Mellitus

1.1.1. Definition, Presentation, and Diagnosis

Diabetes mellitus is a condition with a chronic elevation in blood glucose concentrations which result from a deficiency of the hormone insulin, its secretion, action, or both (Craig et al. 2009). In patients with diabetes, carbohydrate, fat, and protein metabolism are also negatively affected as a result of insulin deficiency.

Diabetes can manifest as type 1 diabetes mellitus (T1DM), which is characterized by an absolute insulin deficiency as a result of autoimmune destruction of β cells in the pancreas, and type 2 diabetes mellitus (T2DM), which is characterized by insulin secretion and resistance to insulin action (American Diabetes Association (ADA)), Diabetes Care 2008, Bilous et al. 2010). The majority of childhood diabetes is T1DM.

The most common symptoms of T1DM are polyuria, polydipsia, and polyphagia. Other symptoms include blurred vision, weight loss in association with glycosuria and ketonuria, abdominal pain (Craig et al. 2009), fatigue and changes in character (Bilous et al.2010)

Children with T1DM usually present with these characteristic symptoms (Craig et al. 2009). The onset of the illness can be sudden and often presents with diabetic ketoacidosis (Wolfsdorff et al. 2009).

Diagnosis of diabetes can be made on the basis of blood glucose readings with or without diabetic symptoms (ADA Diabetes Care 2009; WHO 1999). There are three different ways for diagnosis (Table 1).

Table 1: Criteria for the diagnosis of diabetes mellitus (ADA Diabetes Care 2009, WHO 1999)

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L).* Fasting is defined as no caloric intake for at least 8 hours.
2. Symptoms of hyperglycemia and casual plasma glucose ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since the last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test.* The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

1.1.2. Epidemiology and Incidence

In children and adolescents, T1DM is one of the most common endocrine disorders (Danne et al. 2007), which manifests most frequently in early childhood, although onset can occur at any age (Danne et al. 2007, Alemzadeh et al. 2011). T1DM represents over 90% of pediatric diabetes in most Western countries (Craig et al. 2009, Thunander et al. 2008, Vandewalle et al. 1997), although T2DM is becoming more common, especially in certain at-risk populations (Pinhas-Hamiel et al. 2005). The worldwide incidence of T1DM in children aged less than 15 years is increasing steadily, with an average increase of approximately 3% and significant geographical variation (DIAMOND Study 2006). The highest incidence and prevalence of pediatric T1DM is in Finland and Sardinia and the lowest in China. There is a trend with a “North-South” divide, with higher incidence rates in the Scandinavian countries and lower incidence in the southern countries (with the exception of Sardinia) (Craig et al. 2009, ISPAD Guidelines 2009). A two-fold increase in new cases in children younger than 5 years of age is expected by 2020 (ISPAD Guidelines 2009, DIAMOND Study 2006, EURODIAB Study 2009). According to current German estimates, there are 21,000–24,000 children and adolescents aged 0–19 with T1DM (Rosenbauer 2002, Neu et al. 2002, Ehehalt et al. 2008). Unofficial

estimates report even higher numbers in Germany, with approximately 30,000 children with T1DM and 2,500 new onset cases per year. In Germany, the mean age- and sex-adjusted incidence is 15.3 cases per 100,000 individuals per year, and the average increase in the incidence rate is 4.4% (Ehehalt et al. 2012). In Bosnia-Herzegovina, the incidence is considered moderate, with 7.1 cases per 100,000 individuals per year for both sexes, although trend is rising (Tahirovic et al. 2007).

1.1.3. Therapy

Treatment of T1DM is complex and a highly responsible task. Continuous insulin therapy and insulin delivery by pump or injection is necessary for the survival of these patients. Aside from insulin, equally important elements of therapy are a healthy diet, self-monitoring of blood glucose (SMBG), physical activity, and education (Silverstein et al. 2005).

Glycemic control plays an important role in preventing or postponing the onset of long-term diabetes complications in pediatric patients (Danne et al. 2007), and it can be attained using adequate insulin therapy (Soliman et al. 2006, Danne et al. 2007). However, insulin therapy in adolescents needs to aim for glycemic level goals without increasing the rate of hypoglycemia, take into account variations in insulin requirements as a result of hormonal and physiological changes during puberty, and consider psychological and social issues (Danne 2007, Soliman et al. 2006).

Regular and proper application of all therapeutic elements results in near-normal glycemia and sufficient control of the disease. Patients on intensive insulin treatment with good glycemic control can avoid or delay acute and chronic complications (DCCT 1993, DCCT 1994, De Beaufort et al 2007, Lachin et al. 2008) with quality of life comparable to that in non-diabetic individuals (DCCT 1994, Stahl et al. 2012). Therapy for children and young people with diabetes is more demanding than that for adult patients, and require a multidisciplinary diabetes team (ISPAD Guidelines 2009, Silverstein et al. 2005, Danemann 2006) that typically consists of doctors, diabetologists, educated nurses, dieticians, psychologists, a social worker, and specialists from other fields (Silverstein et al. 2005), which could also be pharmacists.

Some of the insulins that are used in the management of T1DM and their action profiles are presented in Figure 1 (Hirsch 2005) and Table 2 (Bangstad et al. 2009).

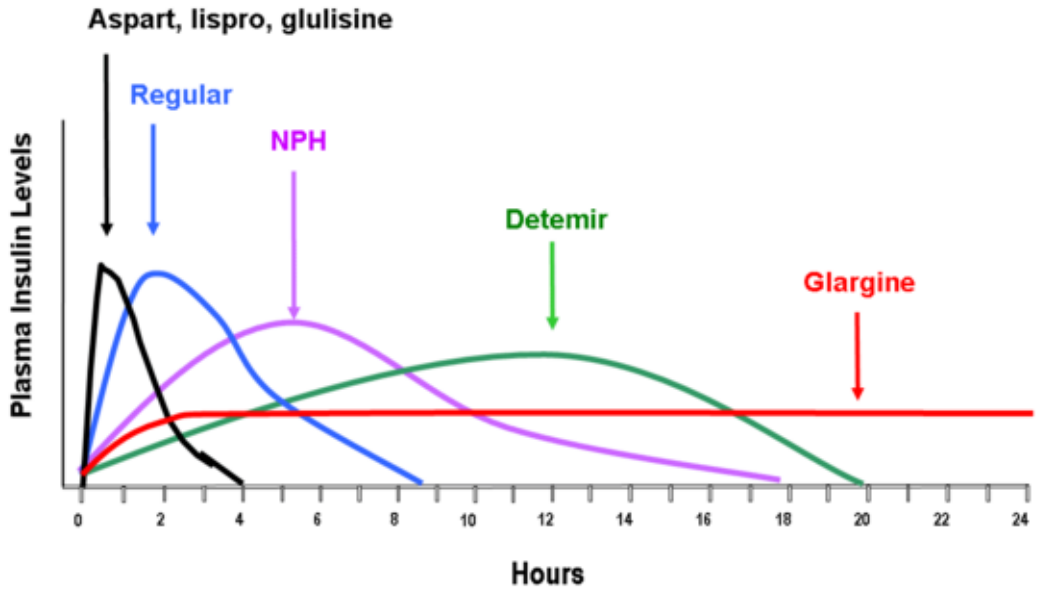


Figure 1: Insulin time-action profiles after subcutaneous injection of insulin aspart, insulin lispro, insulin glulisine, regular insulin, NPH insulin, insulin detemir, and insulin glargine (adapted from Hirsch et al. 2005); *NPH* neutral protamine hagedorn insulin

Table 2: Selected insulin preparations and insulin action profiles (adapted from Bangstad et al. 2009 and ISPAD Guidelines 2009)

Insulin type	Onset (h)	Peak (h)	Duration (h)
Rapid-acting analogs (aspart, glulisine, lispro)	0.15–0.3	1–3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate-acting NPH	2–4	4–12	12–24
Basal long-acting analogs			
Detemir	1–2	6–12	20–24
Glargin	2–4	None	≈24

NPH neutral protamine hagedorn insulin

A basal-bolus regimen, with multiple injections a day (including an injection to cover each meal), is often used as a therapy, trying to simulate the physiological insulin supply seen in a healthy, non-diabetic individual. The basal-bolus principle (i.e. insulin pump or or long-acting insulin/basal analog once or twice daily and rapid-acting boluses with meals and snacks) provides the closest match to physiological insulin delivery. (Bangstadt et al. 2009, ISPAD Guidelines 2009).

ISPAD clinical practice consensus guidelines 2009 in children and adolescents (Bangstadt et al. 2009) recommend the following daily insulin dosages:

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 IU/kg/day.
- During puberty, requirements may rise substantially above 1 and even up to 2 IU/kg/day.

Patients in the prepubertal stage are usually well regulated with 0.7–1.0 IU/kg/day. During puberty, because of the high activity of counter-regulatory hormones and insulin resistance, the relative need for insulin increases to 1.0–1.8 IU/kg/day. Upon completion of the growth and development phase, insulin doses are stabilized at about 0.8–1.0 IU/kg/day (Danne et al. 2007).

1.1.4. Acute and Long-Term Complications

Persistently elevated blood glucose levels of blood glucose, often seen during adolescence and puberty, often result in acute and long-term diabetic complications. These complications represent a major economic burden for healthcare systems, mainly as a result of hospitalizations and drugs costs (Petersen 2010, Franciosi et al. 2013). Therefore, it is important to employ care strategies to improve disease management and glycemic control in order to prevent diabetes complications and reduce long-term costs (Franciosi et al. 2013). One of those strategies of care could be pharmaceutical care.

1.1.4.1. Acute Complications

- **Diabetic Ketoacidosis (DKA)**

Even with adequate management, diabetic ketoacidosis is one of the most serious and potentially life-threatening acute complications of diabetes. DKA is caused by an absolute insulin deficiency accompanied by a concomitant increase in counter-regulatory hormones (catecholamines, glucagon, cortisol, and growth hormone) (Wolfsdorf et al. 2009, ISPAD Guidelines 2009, Kitabchi et al. 2006). Patients not previously diagnosed with T1DM often present with DKA at diagnosis (Wolfsdorf et al. 2009). DKA can rapidly occur in patients who skip their insulin therapy for any reason, especially the long-acting insulin (Hanas et al. 2009), or in insulin pump users if the supply of insulin is interrupted (Hanas et al. 2009). Periods of increased stress (e.g. sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting) are linked with elevated levels of counter-regulatory hormones, causing relative insulin deficiency (Wolfsdorf et al. 2009).

DKA has a high and stable prevalence in pediatric T1DM of around 30% (Dabelea et al. 2014). Prevalence is the highest in patients aged 0–4 years (around 39%) and decreases with increasing age (Dabelea et al. 2014). Higher prevalence was associated with younger age at diagnosis, low income, and a lack of access to medical care (Dabelea et al. 2014, the SEARCH for Diabetes in Youth Study).

DKA in children and adolescents is a medical emergency and requires urgent action by an experienced diabetes team and admission to hospital. (Abdelghaffar 2013). Intravenous rehydration and insulin infusion should be initiated as soon as possible. It is therefore of utmost importance to increase access to healthcare providers, educate patients and the general population regarding the signs and symptoms of DKA (Table 3), and increase awareness, including at the time of first diagnosis.

Table 3: Clinical manifestations of diabetic ketoacidosis (Wolfsdorf et al. 2009, ISPAD Guidelines 2009)

Dehydration
Rapid and deep sighing (Kussmaul respiration)
Nausea, vomiting, and abdominal pain mimicking an acute abdomen
Progressive obtundation and loss of consciousness
Increased leukocyte count with left shift
Non-specific elevation of serum amylase
Fever only when infection is present

- **Hypoglycemia**

Hypoglycemia is one of the most common acute complications of the treatment of T1DM (Clarke et al. 2009). The perception of hypoglycemia can differ between individuals. Therefore the values of hypoglycemia are not uniformly defined. However, the American Diabetes Association (ADA) (Workgroup on Hypoglycemia, ADA 2005) defines hypoglycemia as BG below the threshold value of 70 mg/dL (3.88 mmol/L), in all age groups, along with typical symptoms (Table 4). Children may also exhibit behavioral or mood changes as a result of hypoglycemia, such as irritability, erratic behavior, nightmares, and crying (McCrimmon et al. 1995). A change in behavior associated with hypoglycemia is also common in adolescents.

Table 4: Typical symptoms of acute hypoglycemia (Bilous et al. 2010)

Autonomic symptoms	**Neuroglycopenic signs**	**Malaise**
Diaphoresis	Confusion	Headache
Pounding heart	Slurred speech	Nausea
Hunger	Drowsiness	
Shaking (tremor)	Disorientation	
	Irrational or uncontrolled behavior	

The physiological response of the body to declining BG concentration is to reduce insulin secretion, followed by the release of glucose counter-regulatory hormones (Figure 2). This is known as an adrenergic response (via glucagon and epinephrine), which activates the autonomic symptoms (Table 4) as physiological early warning system to restore BG (i.e. by carbohydrate intake). If the BG falls further (to approximately <50 mg/dL or 2.8 mmol/L), neuroglycopenic symptoms (Table 4) with impaired brain function present and, in the case of severe and prolonged hypoglycemia, coma and death may also occur (Harisson's Internal Medicine, 2011).

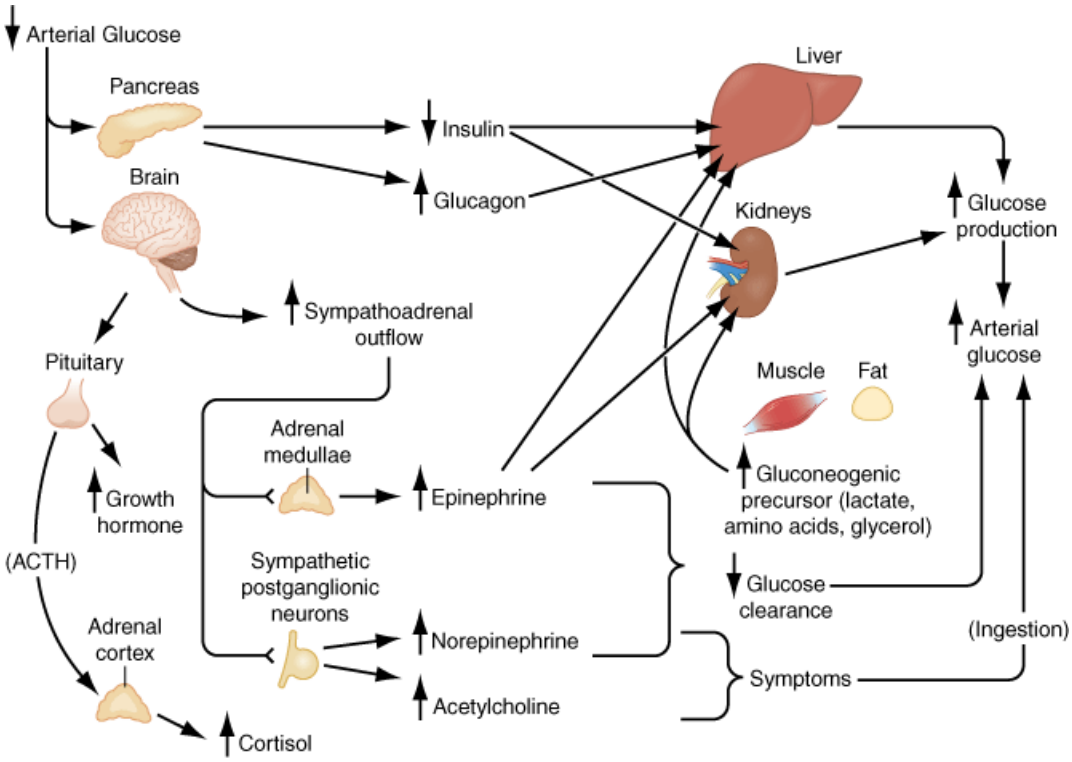


Figure 2: Physiology of glucose counter-regulation, showing the mechanisms that normally prevent or rapidly correct hypoglycemia. In insulin-deficient diabetes, the key counter-regulatory responses (i.e. those that suppress insulin and increase glucagon) are lost, and stimulation of the sympathoadrenal outflow is attenuated (Fauci et al. Harisson's Principles of Internal Medicine, 17th edition. Copyright Mc-Graw-Hill, 2008; Reproduced with permission of Mc-Graw-Hill Education)

The principle treatment for hypoglycemia is administration of rapidly-absorbed carbohydrates to quickly increase BG and reduce hypoglycemia symptoms. The recommended treatment is 15 g for a 50 kg child (approximately 0.3g/kg) of rapidly-

absorbed carbohydrates, such as glucose tablets or a drink or juice containing sugar (Clarke et al. 2009, ISPAD guidelines 2009). BG should be re-tested after 15–20 min, and if there is no improvement, the oral carbohydrate treatment should be repeated and BG re-tested in another 20–30 min.

Even an episode of mild hypoglycemia can cause changes in cognitive function, attention, learning, and thinking speed. Some cognitive deficits may persist beyond the acute phase of hypoglycemia. Frequent hypoglycemia and severe hypoglycemia episode have been associated with cognitive impairments in children and adolescents with T1DM (Hannonen et al. 2003) particularly if they were diagnosed before 5 years of age (Ryan et al. 1985, Schoenle et al. 2002).

Diagnosis of hypoglycemia should be made in accordance to the “Whipple's Triad” (Whipple 1938), and the following three criteria must be met (Workgroup on Hypoglycemia, ADA 2005):

1. low blood glucose concentration;

2. typical symptoms at the time of hypoglycemia;

3. improvement after intake of carbohydrates.

- **Severe Hypoglycemia**

Severe hypoglycemia, according to the ADA definition, is an event requiring the assistance of another person to administer glucagon (subcutaneously or intramuscularly), carbohydrates, or other resuscitative actions. Severe neuroglycopenia can lead to seizure or coma. BG measurements may not be available during such an event; however, neurological recovery after BG is restored to normal provides sufficient evidence that the event was induced by low BG concentration (Workgroup on Hypoglycemia, ADA 2005).

Every hypoglycemic event requires a detailed assessment by pharmacists and other healthcare professionals in order determine the cause, which could be an excessively high dose of insulin (i.e. not taken with food) or physical activity (Clarke et al. 2009). The following assessment should be performed together with the patient: if inadequate carbohydrates were taken; if the time between insulin injections was too short; and

whether there is hypoglycemia unawareness, vomiting, diarrhea, gastroparesis, physical activity, or alcohol consumption.

Hypoglycemia is a significant mortality factor in patients with diabetes (Edge et al. 1999, Soltez et al. 1998), and nocturnal hypoglycemia is the suspected cause of death in young patients with T1DM, known as the “dead in bed” phenomenon (Gill et al. 2009). Because of a fear of hypoglycemia, patients (and in particular their parents) deliberately maintain higher BG levels; this is even more likely if the patient is small and has a history of hypoglycemia (Clarce et al. 1998). To overcome this fear, pharmacists and other healthcare professionals must work intensively and raise hypoglycemia awareness both with the parents and the patients.

1.1.4.2. Long-Term Complications

- **Micro- and Macrovascular Complications**

T1DM complications can also include microvascular and macrovascular disease, which are major causes of morbidity and mortality (Harjutsalo et al. 2011, Laing et al. 2003). One of the main challenges in the management of diabetes is finding new approaches to prevent these complications (Danemann et al. 2006).

In childhood and adolescence, clinical manifestation of late diabetes complications are rare (Donaghue et al. 2009). Nevertheless, these patients require intensive education and treatment in order to prevent or delay the onset and progression of complications (DCCT 1994).

Long-term microvascular complications of diabetes include retinopathy, nephropathy, neuropathy, and macrovascular disease. The mortality and morbidity of cardiovascular disease are markedly increased in diabetic individuals compared with the non-diabetic population (Laing et al. 2003).

Among others, risk factors for the development of diabetes complications include longer duration of disease, older age, and puberty (Donaghue et al. 2009).

Therefore, it is of crucial importance and the responsibility of pharmacists and other healthcare professionals to remind the pediatric patients and their parents to regularly screen for complications (Table 5).

Table 5: Recommended screening intervals for diabetes complications in children and adolescents (Donaghue et al.2009, ISPAD guidelines 2009)

Complication	Screening commencement	Screening methods
Retinopathy	Annually , from age 11 years (with 2 years diabetes duration) or from age 9 years (with 5 years duration)	Fundal photography or ophthalmoscopy
Nephropathy	Annually , from age 11 years (with 2 years diabetes duration) or from age 9 years (with 5 years duration)	Albumin/creatinine ratio (urine), morning albumin
Neuropathy	Unclear	History, physical examination
Macrovascular disease	After 12 years of age	Lipid profile every 5 years, blood pressure annually

1.2. Adolescence and Puberty

1.2.1. Transition to Adulthood

Adolescence is a transitional phase of development between childhood and adulthood. It is linked with many challenges specific to the individual, but healthcare teams and families must also face these challenges (Skinner et al. 2000). Therefore, the transition to adult care should be performed smoothly, with a common sense approach and involvement of all healthcare professionals and the family, in order to prevent or postpone diabetic complications. The most appropriate timing for the transition to adult diabetes care should be when the adolescent demonstrates capabilities of effective self-care. The healthcare team should ensure that adolescents do not drop out of their usual care in this transition period (Dannemann 2011). It is conceivable that pharmacists who have cared for young patients during their childhood years could help facilitate this process of transition.

1.2.2. Metabolic Control During Adolescence

Diabetic complications are directly linked to metabolic disorders associated with hyperglycemia (Fowler 2008). Glycotoxicity, or tissue damage caused by excessive glucose, suggests that good glycemic control can prevent microvascular complications (Robertson 2003). Glycemic control is a synonym for the metabolic control of diabetes. HbA1c level is the most useful indicator of metabolic control (Rewers et al. 2009 , ISPAD guidelines 2009) and elevated HbA1c levels over years are linked with late micro- and macrovascular complications (DCCT 1993, DCCT 1994). The recommended target HbA1c level for all age groups is <7.5% (Table 6) (Rewers et al. 2009).

Table 6: HbA1c levels (%)* as indicators of glycemic control (adapted from Rewers et al. 2009, ISPAD Guidelines 2009)

Ideal (non-diabetic)	Optimal	Suboptimal (action suggested)	High risk (action required)
<6.05%	<7.5%	7.5–9.0	>9.0‡

HbA1c glycated hemoglobin
* HbA1c must be adjusted according to individual circumstances; ‡ HbA1c of 8.9% linked to poor outcomes (DCCT); therefore, levels below this value recommended

In many T1DM patients, metabolic control deteriorates during puberty (Mortensen et al. 1998, Dabadghao et al. 2001), and is associated with "poor adherence to complex therapy regimens" (Morris et al. 1997), "insulin misuse, erratic meal and exercise patterns" (Bryden et al. 1999), "hazardous and risk-taking behaviors" (Skinner et al. 2000), and "physiological changes in puberty, which lead to greater insulin resistance" (Amiel et al. 1986) . Increased insulin resistance and "Dawn-Phenomenon" occur through increased growth hormone and sex steroid hormones secretion but also through therapy errors, and a desire for full flexibility without the necessary dose adjustment or problems of transition of diabetes therapy from parents to adolescents.(Holl et al.2013) These facts pose great challenges on the diabetic healthcare team and the family of the patient. Therefore, extending the provider outreach (i.e. by including pharmacists) in the care of adolescents is a sensible approach to improve glycemic control and prevent or delay micro- and macrovascular complications.

1.3. Pharmaceutical Care

1.3.1. Definition

Pharmaceutical care is a widely used term, and its most well-known definition was given by Heppler and Strand as “the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient’s quality of life” (Heppler et al. 1990). This definition was a new approach to the pharmacists’ profession and responsibilities. A further expansion of this definition is that pharmaceutical care includes responsibilities, medication surveillance, counseling, and evaluation of all outcomes of care (van Mill et al. 2004). However, since 1990 there has been much debate regarding the understanding of this definition and on how it is connected with the pharmacist’s professional mission (van Mill et al. 2013). Pharmaceutical care approach involves pharmacists closely collaborate with the patients and other healthcare professionals in designing, implementing, and monitoring a therapeutic plan, in order for the patient to achieve optimal outcomes (Cipolle et al. 1998).There are three major steps in this process, namely identifying, resolving, and preventing drug-related problems (DRPs) (Cipolle et al. 1998).

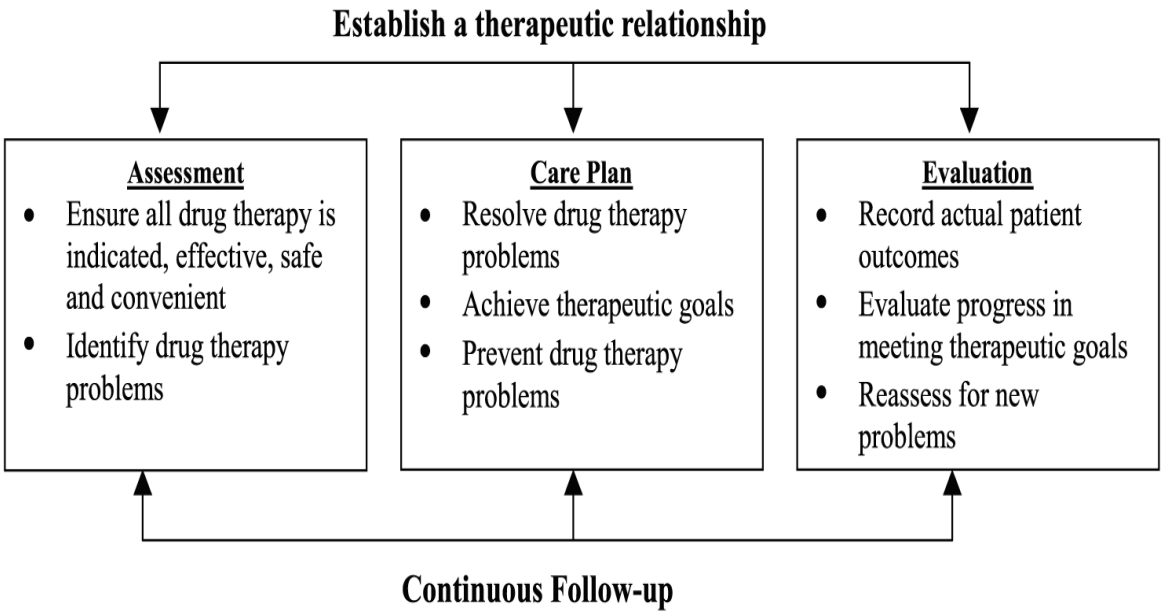


Figure 3: Pharmaceutical care process (Cipolle et al. 1998)

In the pharmaceutical care process (Figure 3), pharmacists assess the patient in terms of DRPs and drug therapies that may have caused the problems, and develop a care plan and perform follow-up evaluations (Cipolle et al. 2004). Pharmacists who deliver pharmaceutical care take responsibility for optimization of the patient's drug therapy.

1.3.2. Documentation in Pharmaceutical Care

The correct implementation of pharmaceutical care includes documentation of every step of the process (Figure 3). This can be done using a patient care process to develop a patient-specific pharmaceutical care plan (Cipolle et al.2004, Schwinghammer 2011) by utilizing the SOAP method (an acronym for **s**ubjective, **o**bjective, **a**ssessment, and **p**lan).

1.3.2.1. Patient Care Process

The patient care process of the pharmacists according to Cipolle consists of three major steps: (1) assessment of the patient's drug-related needs; (2) development of a pharmaceutical care plan to meet those needs; and (3) follow-up evaluation to assess whether positive outcomes were achieved (Cipolle 2004). A detailed description of the 7-step patient care process (Schwinghammer 2011) is as follows:

(1) Assessment of drug-related needs involves the collection and evaluation by the pharmacist of patient data on drugs and underlying disease. The patient is the "information giver". Pharmacists need to have good communication skills and ask open questions (i.e. "What concerns do you have that we may discuss together today?"). Information can also be obtained from family members, and current and past medical history of the patients can be obtained from physicians. Relevant information includes:

- Patient information (demographics and background information): age, gender, height, weight, social history, family history (including relevant medical histories of the close relatives).
- Disease information: past medical history, current medical problems, history of all present illnesses, review of organ systems, physical examination, laboratory results, medical diagnoses.
- Drug information: allergies and side effects, current prescription medications.

By gathering all this information, pharmacists can identify the patients' drug-related problems (Table 7).

Table 7: The most common drug-related problems (Shargel, 2009)

1. Unnecessary drug therapy
2. Wrong drug
3. Dose too low
4. Dose too high
5. Adverse drug reaction
6. Drug interactions
7. Needs additional drug therapy

(2) Determination of the desired therapeutic outcomes includes avoiding and minimizing side effect of the treatment, reduction or prevention of symptoms, prevention of complications, enhancing quality of life.

(3) Determination of therapeutic alternatives, such as non-drug treatment (i.e. physical activity, diet, use of supplements).

(4) Design of an optimal pharmaceutical care plan, with a goal to finding optimal drug, dosage, schedule, and therapy duration, based on the patient's needs.

(5) Identification of parameters to evaluate outcomes. Pharmacists should be familiar with laboratory and clinical data in order to evaluate if the desired outcome has been achieved, and to assess and prevent adverse drug reactions. Outcome parameters should be specific, measurable, and directly linked to therapeutic goals. For instance, if the goal was to improve glycemic control in a T1DM patient, objective parameters such as HbA1c should be evaluated, and subjective parameters such as wellbeing should be assessed (e.g. the patient is less tired or wakes up fresh and rested).

(6) Patient education. The patient is a partner in the care process, especially in chronic conditions (such as diabetes) where self-management is very important. Pharmacists

need to provide adequate information to the patients in order to increase adherence, to ensure success of treatment and reduce potential side effects.

(7) Communication of the pharmaceutical care plan. This should not only include verbal communication, but written documentation of the plan (i.e. recommendations) is required with physicians and other healthcare professionals. For communication and documentation of the pharmaceutical care plan, a SOAP form can be used, although this form has limitations with respect to certain data elements, such as a lack of the desired therapeutic outcome (Schwinghammer 2011).

S (Subjective data): the pharmacist should gather data related to the identified problem and underlying symptoms from the patient, and record all of subjective information (e.g. 'I have a headache', 'I feel dizzy').

O (Objective data): the pharmacist should collect laboratory test results, perform physical examination if possible, and collect the medical history and medication profile, usually from the healthcare practitioner.

A (Assessment): pharmacists should analyze and integrate the subjective and objective data, evaluate drug therapy, draw conclusions relevant to the identified problem, and develop a plan.

P (Plan): pharmacists should document a plan of action based on observations and information by the healthcare practitioner, such as a plan to optimize drug therapy and provide monitoring of the drug therapy. This can include initiation of new drug therapy or dose change of existing therapy, or ordering new laboratory tests.

1.3.3. Studies of Pharmaceutical Care in Adults with T2DM

Several pharmaceutical care studies with a multidisciplinary approach in adults with T2DM have been carried out worldwide, showing improved HbA1c outcomes. A pilot study with a structured pharmaceutical care approach, which included community pharmacists as members of multidisciplinary teams, found improved HbA1c values, cholesterol levels, and blood pressure in the pharmacist-led group (Wermeille et al. 2004). In a meta-analysis of 302 articles and 108 pharmacists-involved interventions, a

significant improvement in HbA1c was found in the group with pharmacist intervention versus the control group (Machado et al. 2007). The intervention in most of these studies consisted of education and medication therapy management provided by pharmacists. Another systematic review and meta-analysis of 298 randomized, controlled studies found an improvement in health outcomes when pharmacists provided direct patient care on therapeutic, safety, and humanistic outcomes as part of a multidisciplinary team (Chisholm-Burns et al. 2010).

Two large studies of pharmaceutical care have evaluated its impact on clinical outcomes, with reductions in HbA1c ranging from 0.5–1.0%. The first study was conducted in Belgium, and was a 6-month, randomized, controlled, parallel-group trial in 66 community pharmacies, with 153 patients in the intervention group and 135 in the usual care group. This study focused on correct medication use, medication adherence, and promotion of a healthy lifestyle, and found improved outcomes (Mehuys et al. 2011). The second study was conducted in Australia, with a total of 289 patients (149 intervention and 140 control) and 56 participating pharmacies (28 intervention and 28 control) (Krass et al. 2007), and found significant improvements in clinical and humanistic outcomes.

1.3.4. Studies with Pharmacist Involvement in Adolescents with T1DM

However, data on similar approaches with a structured pharmaceutical care plan in adolescents with T1DM remain scarce. A randomized, controlled study in France that performed a reinforced follow-up via telecare in which the pharmacist intervention consisted of downloading and faxing glucometer data to the hospital with 100 T1DM patients (50 intervention, 50 control) aged 8 to 17 years found no significant difference in average HbA1c levels between the two groups after 6 months (Gay et al. 2006).

Another small-scale study conducted in the USA in which pharmacists were trained facilitators and used the novel approach of the US Diabetes Conversation Map program (an ADA-approved tool for providing group education on diabetes self-management programs) to train group leaders as facilitators for their peers (Sims et al. 2011). Data from only six patients were evaluated at the end of the study, and showed an increase in HbA1C with an improvement in adherence to lifestyle modification and health

perception, which affirms the challenge of reaching metabolic control in adolescents with T1DM.

The available evidence in adolescents with T1DM suggests that pharmacists interventions alone, in the absence of a structured pharmaceutical care according to the Standards of Practice (Cipolle et al. 2004) and without proposed responsibilities by pharmacists and patients, medication surveillance, counseling, and evaluation of all outcomes of care (Foppe et al. 2004) may not be sufficient to improve clinical outcomes, such as HbA1c. To date, and to the best of my knowledge, there are no pharmaceutical care studies (as defined by Cipolle et al. 2004) conducted in adolescents with T1DM. Therefore, in the DIADEMA (DIabetes in ADolescence Engagement and Monitoring by phArmacists) study presented in this thesis, the effect of intensive and structured pharmaceutical care on important clinical outcomes in adolescents with T1DM has been explored.

2. Objectives and Outcomes of the DIADEMA Study

Pharmaceutical care as a concept is not widely disseminated in the pharmacy practice, either in Germany or in Bosnia-Herzegovina. The major barriers in implementing pharmaceutical care in most European countries apply to these countries as well, which are a lack of money, pharmacist time, clinical education, communication skills, and the attitude of other professionals (Foppe et al. 2001). Traditionally, the practice of pharmacists in both countries is focused primarily on distributing drugs, in this case insulin and other diabetes-related devices, to diabetic patients (including adolescents with T1DM), with diabetes clinics imparting education on insulin and glucose monitoring.

The aim of this project was to include regular community-based pharmacists, in addition to clinical pharmacists, to provide extended support to adolescents with T1DM. We believe that, as pharmacists are the most accessible healthcare professionals, they are in a unique position to deliver such a structured and multifaceted pharmaceutical care. We also hoped to encourage pharmacists to apply their clinical skills, education, and knowledge in the care of adolescents with T1DM through the use of this program.

It is well known that poor glycemic control during adolescence in many T1DM patients will eventually lead to micro- and macrovascular diabetic complications, increased morbidity, and premature mortality (Dabadghao et al. 2001, Harjutsalo et al. 2011). In addition, various studies have shown that frequent visits and contact with healthcare providers resulted in better metabolic control (Kaufmann et al. 1999, Jackobson et al. 1997). We hypothesized that extending the provider outreach with pharmacists could help to reduce the rate of preventable acute and late diabetes complications.

Thus, we aimed to develop a binational, practice-oriented pharmaceutical care protocol which could be used by both clinical and community-based pharmacists, one that would give the pharmacist a tool to promote better adherence to therapy, and to provide instructions and education to the healthcare teams according to international treatment guidelines.

The DIADEMA study aims to answer following scientific questions.

- Does the pharmaceutical care carried out in accordance to pediatric guidelines improve the following clinical outcomes?
    - Hb1Ac, without an increase in the number of severe and non-severe hypoglycemia events.
    - Patient wellbeing, according to the Wellbeing Index (WHO-5).
    - Satisfaction with pharmaceutical care.
- What is the adherence of the adolescents in the two countries to selected International Society of Pediatric Diabetes (ISPAD) and German Diabetes Society (DDG) pediatric guidelines?
- What are the most common DRPs in adolescents with T1DM?

3. Methods

3.1. Study Protocol

3.1.1. Study Design

DIADEMA was a randomized, controlled, prospective, 6-month, two-center study in adolescents with T1DM and poor glycemic control. The study had two groups, (1) an intervention group, which in addition to usual care, received pharmaceutical care delivered by pharmacists and (2) a control group, which received usual care only. Usual care comprises appointments with diabetologists and diabetes educators, conducted usually every three months in the respective outpatient diabetic clinics. There were two study sites, one in Germany at the outpatient diabetology clinic of the Pediatric Clinic Helios Hospital Krefeld (with 12 community pharmacies) in Krefeld and its surrounding area, and one in Bosnia-Herzegovina at the outpatient diabetology clinic of the University Pediatric Clinic in Sarajevo. In Germany, one physician (pediatric diabetologist), one diabetic educator (study nurse), and 14 community-based study pharmacists participated, whereas in Bosnia the diabetic study team consisted of one physician (pediatric diabetologist), one diabetes educator (study nurse), and one clinical pharmacist (the author of this thesis). The study protocol was developed at the Heinrich-Heine University Institute of Clinical Pharmacy and Pharmacotherapy under the supervision of the project leader of the DIADEMA study, Prof. Dr. med S. Läer.

3.1.1.1. Ethical Approval

The study received ethical approval from the Ethics Committee of the medical faculty of Heinrich-Heine University, Düsseldorf, Germany (No. 3991). According to the Agency for Drugs and Medical Devices of Bosnia-Herzegovina (Agencija za lijekove Bosne i Hercegovine; reference number 10-07-56-1207/12), this study did not qualify as a clinical trial (Official Gazette Bosnia-Herzegovina 2010; Nr. 4/10), the agency was not responsible for oversight of this kind of research and approval was not required. Thus Ethics Committee of the Clinical Center also did not require ethical approval as this study did not qualify as a clinical trial (Clinical Trials and Medical Devices Directive of Bosnia-Herzegovina 2010). Study patients and their parents or legal guardians were

verbally informed of study procedures and were provided with the information leaflets (Attachment 1) by diabetologists and diabetes educators. Patients and their parents or legal guardians signed the informed consent form (Attachment 2) prior to participating in the study. Patients were given at least two days to reflect and make a decision regarding participation in the study.

According to Good Clinical Practice (GCP), the "rights, integrity, and confidentiality of trial subjects were protected" (International Conference on Harmonization [ICH]-GCP 2002). To conform to the "uniformity of the performance of the pharmaceutical care process", Standard Operating Procedures (SOPs) (Attachment 3) with detailed, written instructions were provided to pharmacists and physicians (ICH-GCP 2002). Adverse Events (AE) were documented (Attachment 4) and serious AEs (SAEs) (Attachment 5) were documented and reported to the study leader and to the Ethics Committee within 24 hours of occurrence. Pharmacists, diabetologists and diabetes educators were provided with a brief instruction manual on the data flow of the DIADEMA Study (Attachment 6).

3.1.1.2. Recruitment and Randomization

Eligible patients were recruited by the clinics in Germany and in Bosnia-Herzegovina. In Germany, patients willing to participate were asked to provide the names of their regular, nearby community pharmacies, where they usually obtain insulin and other diabetes devices. Fourteen of these community-based pharmacists were approached to participate as study pharmacists, and all were recruited. No additional specialization in diabetes pharmaceutical care was required. The community-based pharmacists received both individual and group training provided by the study co-ordinators (M. Krueger and E. Obarcanin) on GCP, DIADEMA study protocol, case report forms (CRFs) and documentation, pharmaceutical care and development of pharmaceutical care plans, and pathophysiology management of T1DM. Individual training was provided before the study and group training was provided at regular DIADEMA team meetings, which took place before and every two months during the study. During the study, pharmacists could contact the study leader (E. Obarcanin) via phone or email anytime, if needed.

Because no data were available regarding the effect size of a pharmaceutical care intervention in adolescents with T1DM, and as only a small sample size was available at each site (due to the strict inclusion criteria), we performed a post hoc power analysis based on the actual sample and effect using GPower version 3.1. (Faul et al. 2007).

Randomization was performed by diabetes educators (nurses) using a simple, easy-to-implement, and well analyzed coin-toss method (Blume et al. 2004, Berger 2006). This method was chosen for practical, organizational and coordination reasons as the exact same, feasible and practical method needed to be used in both centers. Physicians supervised the coin toss to avoid potential bias (Clark et al. 2009). Before tossing the coin, nurses wrote eligible patient names on paper and sealed these in envelopes to conceal allocation and minimize selection bias (Berger 2006, Viera 2007). The coin toss resulted in 40 “tails”, pre-designated as the intervention group and 29 “heads”, pre-designated as the control group. Given the small sample size, the randomization resulted in unequal numbers of patients in the groups. However, the use of unequal randomization ratios significantly reduce study power only if the ratio is 3:1 or more (Pocock 1995, Gail et al. 1976, Dumwille 2006), which is not expected in our study as it has app. 4:3 ratio between the groups. Following randomization, all envelopes containing patient names in each group were consecutively numbered by the nurses before being opened. To improve willingness to participate, patients who consented verbally were randomized, and then signed consent prior to the study start.

3.1.1.3. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the DIADEMA study were as follows.

Inclusion criteria:

- adolescents at 12–18 years of age;
- confirmed diagnosis of T1DM at least 6 months prior to study enrolment;
- use of at least 0.5 IU/kg/day of insulin (as an indicator that patients were outside of the remission or “honeymoon” phase);

- use of intensified conventional therapy (ICT) or continuous subcutaneous insulin infusion (CSII);
- HbA1c consistently over 7.5% (from at least two measurements taken at least 3 months apart).

Exclusion criteria:

- intellectual disability;
- developmental disorders;
- drug abuse;
- psychiatric conditions;
- pregnancy and breastfeeding.

3.1.2. Pharmaceutical Care of Adolescents with T1DM

3.1.2.1. Visits to the Diabetes Clinics

All study participants attended the diabetes clinics at the beginning of the study (baseline visit), after 3 and after 6 months, to receive usual care (usually performed every three months), including HbA1c measurement and counseling by the diabetes team. During these three visits, diabetes educators (study nurses) collected sociodemographic patient data, such as age, sex, history of present illness, concomitant disease, and clinical data (in particular HbA1c, BG, cholesterol and triglyceride levels).

To facilitate data exchange in the DIADEMA study, a two-part case report form (CRF) was employed. Study nurses entered coded and blinded clinical data into standardized Physicians CRFs (Attachment 7). In Germany, the Physicians CRFs were faxed to the pharmacists, whereas the clinical pharmacist in Bosnia-Herzegovina had on-site access to these forms. In this manner, patient data was exchanged between the physician, diabetic educators and the pharmacists in Germany. After 3 and 6 months of the study, pharmacists received clinical data from the respective clinics, particularly the HbA1c values, in order to monitor the progress of the pharmaceutical care intervention.

3.1.2.2. Intervention Group

Participants attended pharmacists in the community pharmacies in Germany or in the clinical pharmacist's office in the outpatient clinic in Bosnia-Herzegovina once a month for 6 months for scheduled pharmaceutical care visits. The visits lasted 60–90 min. Additional on-demand phone calls and visits were performed if required by the patients to adjust their BG in special situations, such as school excursions, severe hypoglycemia, or sports, or at the discretion of the pharmacist.

3.1.2.3. Patient Blood Glucose Diaries

In order to receive pharmaceutical care from their pharmacists, patients in the intensive care group had to record in detail their BG measurements, preferably for a whole week before the pharmaceutical care visit. If this was not possible, then measurements from the previous 24 hours were required. The BG diaries served as a basis for communication between patients and pharmacists, and contained the following details (Rewers et al. 2009, ISPAD Guidelines 2009), as well as time and date of BG levels:

- insulin dosage;
- note of special events affecting glycemic control (e.g. illness, parties, exercise, menses);
- hypoglycemic episodes with a description of severity, especially if the help of another person was needed (i.e. severe hypoglycemia);
- alterations in the usual routine that may have caused the event;
- episodes of ketonuria as measured by urine testing strips for ketone testing.

Furthermore, the BG diaries were used by the pharmacists to define strategies to improve outcomes, and were used to empower patients to analyze and discuss their BG readings and to identify the cause for any changes in glycemic control.

3.1.2.4. Patient Education (All Visits)

Patient education consisted of verbal discussions of standardized T1DM-related topics, according to the German Program for National Treatment Guidelines, 2012 (Attachment 14). The topics with special consideration in the adolescent population included:

- the use of insulin and its adjustment in special situations (e.g. disco, sleeping in);
- the importance of SMBG at least four times daily (Rewers et al. 2009, ISPAD Clinical Practice Consensus Guidelines 2009);
- discussion of individual treatment goals according to treatment guidelines;
- prevention of acute complications;
- physical activity;
- problem-solving strategies for special situations;
- sexuality, contraception, menstruation, and family planning;
- tobacco, alcohol, and drug use;
- Annual check-ups and prevention of long term-complications.

All the topics were addressed by the pharmacists at least once during the six visits; some topics were repeated in every visit, such as individual treatment goals and insulin use and its adjustment in special situations.

3.1.2.5. Pharmaceutical Care Intervention (All Visits)

At the first pharmaceutical care visit, pharmacists conducted an extensive interview with the patients, in most cases with the parents, in order to become familiar with the patients and their social environment. At each of the six visits, pharmacists also collected and recorded clinical data, such as measured or documented BG, number of hypoglycemia events in the past month (from patient records), ketone values, insulin

therapy (including dose and side effects), and other data such as carbohydrates intake, nutrition, and physical activity. The tasks at each of the pharmaceutical care visits are summarized in Table 8.

Table 8: Pharmacist intervention and the course of pharmaceutical care visits

Intervention	Pharmaceutical care visits					
	1	2	3	4	5	6
CRFs with clinical data	✓	✓	✓	✓	✓	✓
Evaluation of BG records	✓	✓	✓	✓	✓	✓
Evaluation of HbA1c	✓		✓			✓
PCPs	✓	✓	✓	✓	✓	✓
PCP discussion with physicians[a]			✓			✓
Follow-up and evaluation		✓	✓	✓	✓	✓
Wellbeing (WHO-5) questionnaire	✓		✓			✓
Satisfaction with PhC questionnaire			✓			✓
DRPs list*	✓					
Adherence with selected diabetes guidelines	✓		✓			✓

BG blood glucose, *CRFs* case report forms, *DRPs* drug-related problems, *HbA1c* glycated hemoglobin, *PCP(s)* pharmaceutical care plan, *PhC* pharmaceutical care

[a] PCP could be discussed with physicians at every visit if needed

* This item could be assessed at any visit

The pharmaceutical care intervention was standardized in both countries according to the Standards of Practice (Cipolle et al. 2003). At each visit, pharmacists assessed the patient's drug-related needs by collecting and interpreting clinical data (i.e. HbA1c, number of hypoglycemia events) and BG records from patient diaries (Rewers, 2009, ISPAD Guidelines 2009). Patients in the intervention group measured and documented their BG at least four times daily (i.e. fasting, in response to the action profiles of insulin at anticipated peaks and troughs of insulin action, bedtime) (Rewers et al. 2009), preferably 5–6 times to include measurements 2 hours after meals or during or after

sports. Based on data and evaluation of BG records, DRPs (e.g. insulin non-adherence at school, incorrect insulin dose) were identified at each visit. For each patient, pharmacists developed pharmaceutical care plans (Attachment 9) by applying the educational topics (Attachment 14) listed above and proposed interventions to resolve the problems (e.g. insulin dose adjustment, involving school teachers to facilitate insulin administration at school). At least two measurable individual goals (e.g. hyper- and hypoglycemia reduction in 1 month, HbA1c reduction in 3 months) were defined and discussed with the patient to improve acceptance. The written pharmaceutical care plans were submitted to physicians at visits 3 and 6, and discussed at the regular bimonthly DIADEMA team meetings. Immediate insulin dose changes were proposed verbally to the physicians, although the ultimate decision to change the insulin dose was made by the physicians. Follow-up of patient compliance with insulin therapy, potential complications, and disease control was performed at each return visit, using objective (such as Hba1c, BG) and subjective data. Evaluation of patient progress in achieving individualized goals and assessment for any new problems were performed at each return visit. A strong emphasis on patient empowerment was maintained by the pharmacists, with a transition to self-management of diabetes, depending on the stage and development of the adolescent.

3.1.2.6. Questionnaires (Visits 1, 3, and 6)

In addition to the tasks described above, pharmacists used questionnaires to define quality of life using the Wellbeing Index (WHO-5) at visits 1, 3, and 6 (Attachment 11). At visits 3 and 6, pharmacists provided patients with questionnaires regarding their satisfaction with pharmaceutical care services. Also, during one random visit (from visits 1, 3, or 6), pharmacists recorded the most common DRPs experienced by the patients and checked adherence with selected pediatric guidelines (ISPAD Guidelines 2009, DDG Guidelines 2010).

3.1.2.7. Documentation of the Pharmaceutical Care Intervention

All six pharmaceutical care visits were documented by pharmacists using the Pharmacist CRFs, which were specifically designed for the DIADEMA study (Attachment 8).

For the assessment of individual goals and progress in achieving those goals, a special pharmaceutical care plan form was used (Attachment 9). Follow-up, evaluation, and additional remarks such as communication with physicians and diabetes educators regarding the pharmaceutical care plans or insulin dose change were recorded on the PCP "Additional Comment Form" (Attachment 9). For documentation of patient education during the pharmaceutical care visits, pharmacists could tick a box to indicate which topics were covered and in which visits (Attachment 14). To name and identify DRPs, we used a modified DRP list according to Shargel et al. 2009 (Table 7) in order to relate all DRPs to the underlying T1DM diagnosis (Attachment 12).

The questionnaires to define patient wellbeing (WHO-5) (Attachment 11) and satisfaction with pharmaceutical care services (Attachment 10) were completed and documented, as well as adherence with selected pediatric guidelines (Attachment 13).

3.1.3. Control Group

Patients in the control group had scheduled clinic appointments every 3 months (baseline, month 3 and month 6) to receive usual care by the clinic. Usual care encompassed the measurement of HbA1c and counseling from diabetologists and diabetes educators regarding their BG and diabetes management. Documentation of the clinical data was performed by diabetes educators using the Physician CRFs (Attachment 7). As part of the "usual care visits" in the clinics, patients were advised to measure their BG at least four4 times daily (Rewers et al. 2009) and the frequency of BG monitoring was routinely documented by diabetes educators (nurses).

During the study, patients in the control group did not have contact with study pharmacists. Nevertheless, the control patients could have requested counseling from their local pharmacists where they usually obtain their insulin and other supplies, especially in special situations (e.g. school excursions, hypoglycemia, and occurrence of other concomitant diseases). However, as these local pharmacists were not study participants, we could not confirm if counseling was requested or received.

3.2. Clinical Outcomes

3.2.1. Primary Outcome: HbA1c in the Intervention and Control Groups

HbA1c is formed when glucose becomes irreversibly bound to hemoglobin during the life cycle of circulating erythrocytes (approximately 120 days) (Rewers et al. 2009, ISPAD Guidelines 2009). Physiological and psychological changes during adolescence and puberty negatively affect glycemic control, and result in higher HbA1c levels that are at least 1% higher than those seen in adults (DCCT 1993). Chronic elevations in HbA1c are a predictor of long-term microvascular and macrovascular complications (DCCT 1994). We selected HbA1c to assess glycemic control as it is a widely used measure of optimal glycemic control; other measures include documented hypoglycemia, type of treatment, patient age, and quality of life (Rewers et al. 2009, ISPAD Guidelines 2009).

Thus, the main question of the study was if an intensive and structured pharmaceutical care intervention can improve glycemic control (assessed by the change in HbA1C) relative to usual care. The primary endpoint was the change in HbA1c values from baseline to 3 and 6 months in the intervention group compared with that in the control group.

At baseline and after 3 and 6 months of the study, blood samples were taken from the patients to determine HbA1c values as part of routine care visits in the diabetes clinics. Analysis of the blood samples was performed by the central laboratories of the University Pediatric Clinic in Sarajevo, Bosnia-Herzegovina and of the Helios Clinic in Krefeld, Germany. The HbA1c values were provided to the study pharmacists and served as a basis for patient recruitment (only patients with HbA1c ≥7.5% were eligible) and for assessing the progress of pharmaceutical care intervention during and after the study.

In total, HbA1c values were measured three times per patient, at baseline (up to 1 month prior to study enrolment), after 3 months and after 6 months. This frequency is the same as that typically used in the routine care of adolescents with T1DM.

3.2.2. Long-Term Effect on HbA1c

Although it was not originally planned in the study protocol, HbA1c was measured again, approximately 12 months after the beginning of the DIADEMA study, to test whether the benefit of pharmaceutical care was sustainable beyond the conditions of the study.

3.3. Secondary Outcomes

Of all the secondary outcomes, only severe hypoglycemia was assessed in both study groups; the other secondary outcomes were assessed in the intervention group but not in the control group, as intense monitoring is not part of routine patient care.

3.3.1. Severe Hypoglycemia

Severe hypoglycemia is defined by the ADA (Workgroup on Hypoglycemia 2005) as an event requiring the assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative action (i.e. putting the patient in a stable recovery position, calling an ambulance). Severe hypoglycemia events were recorded by diabetes educators (study nurses) in the clinics from multiple sources (e.g. medical records, number of hospitalizations due to severe hypoglycemia, patients' BG records, and glucometer data). These events were analyzed and compared between the groups for the 6 months prior to the study through retrospective analysis of medical records, as well as during the 6-month study period.

It is well established that a reduction in HbA1c is associated with an increase in severe hypoglycemia episodes (DCCT 1993, DCCT 1994). In pediatric T1DM, severe hypoglycemia is a significant cause for morbidity and occasional mortality (Gill et al. 2009, Weston et al. 1999). Therefore, the aim of the DIADEMA study was to decrease HbA1c through pharmaceutical care intervention, without increasing the rate of severe hypoglycemia episodes.

3.3.2. Non-Severe Hypoglycemia

Non-severe hypoglycemia is defined by the ADA as "documented symptomatic hypoglycemia", an event with plasma glucose concentration of ≤70 mg/dL (≤3.9 mmol/L) (Workgroup on Hypoglycemia 2005) and typical hypoglycemia symptoms (e.g. trembling, sweating, headache, hunger, and blurred vision). The mean number of non-severe hypoglycemia events was recorded by diabetic educators from patients' BG records and glucometer data. These hypoglycemia data collected were quantified 1 month prior to the study, and during months 3 and 6 of the study.

In order to identify hypoglycemia events, patients were advised to perform self-monitoring of blood glucose (SMBG) using their devices, which were previously selected by their diabetologists. The SMBG device had to show precise and accurate BG measurements (Rewers et al. 2009). SMBG had to be performed at least four times a day at different times, such as fasting BG, to include insulin peaks and troughs (e.g. after administering insulin and 2 hours after meals), in association with physical activity, and during the night (Rewers et al. 2009, ISPAD Guidelines 2009, Hermansson et al. 1986). In order to confirm hypoglycemia, the BG tests were performed by patients using the finger tips without using other sites, because alternative sites may be slower in indicating hypoglycemia (Rewers et al. 2009).

As the goal of the study was to improve HbA1c with pharmaceutical care intervention without increasing the rate of hypoglycemia, this secondary outcome was particularly important. Upon discovery of hypoglycemia by SMBG, patients were advised by the pharmacists to treat immediately with a quantity of oral, rapidly absorbed, simple carbohydrate so that BG is increased to 5.6 mmol/L (100 mg/dL) (Clarke et al. 2009).

During pharmaceutical care visits, pharmacists paid particular attention to increase patient awareness of hypoglycemia and hypoglycemia prevention. Pharmacists stressed the importance of the frequent use of SMBG, as early detection may prevent potential serious and severe hypoglycemia events.

3.3.3. Satisfaction with Pharmaceutical Care

A 7-item questionnaire designed by Simon (Dissertation 2009), based on a validated instrument (Larson et al. 2002), was further adapted to T1DM and insulin therapy, as a validated instrument in T1DM does not exist. The seven questions were designed to elicit information on patient satisfaction with pharmaceutical care in general, accessibility of the study pharmacist, pharmacist time devoted to the patient, education on insulin, its side effects and interactions, physical activity, carbohydrates intake, individual treatment goals, and general perception of the pharmaceutical care service and its influence on glycemic control (Attachment 10). The questionnaire was completed by the patients at visits 3 and 6. Patients indicated their satisfaction on a 6-point Likert scale, ranging from 0 (no, not at all, no satisfaction) to 5 (yes, very good, excellent satisfaction), with total scores ranging from 0 to 35. The total scores at visits 3 and 6 were compared for any change in satisfaction with pharmaceutical care over the course of the study.

3.3.4. Wellbeing Index (WHO-5)

The WHO-5 Wellbeing Index is a 5-item questionnaire to determine current patient mental wellbeing over the previous two weeks (WHO-5 Wellbeing Index 1998). It is a valuable assessment tool of emotional functioning and a good screening tool of depression. The items of the questionnaire focus on positive rather than negative aspects of patient life, containing five questions with the following positive wording: “I have felt cheerful and in good spirits”, “I have felt calm and relaxed”, “I have felt active and vigorous”, “I woke up feeling fresh and rested”, and “my daily life has been filled with things that interest me” (Attachment 11). Patients were asked by pharmacists to complete the questionnaire at baseline (visit 1), visit 3, and visit 6. A 6-point Likert scale from 0 (no, not present) to 5 (yes, constantly present) was used to measure wellbeing in the previous two weeks. Total scores were multiplied by four to provide a percentage score of 0–100, with higher scores indicating better wellbeing. Scores <50% are indicative of low mood and scores <28% suggest possible depression. A repeated score of <28% on at least two visits during the DIADEMA study resulted in the patient’s physician being informed and a clinical psychologist being consulted if necessary. A

change of 10% between individual wellbeing scores is regarded as clinically significant. (WHO-5 Wellbeing Index 1998)

By discussing the WHO-5 score with the patients in a constructive and non-judgmental way, pharmacists had a valuable tool with which to emphasize the importance of wellbeing in diabetes self-management, to address potential psychological issues of adolescents, and to include other healthcare professionals (i.e. psychologists) if deemed necessary. Patients were actively engaged to comment on the scores and to propose strategies for improvement.

3.3.5. Drug-Related Problems

The list of most common DRPs (Table 7) (Shargel et al. 2009) was adapted for the purpose of this study and relates all DRPs to T1DM, as the adolescents in our study had only one or two co-morbid conditions and no history of polypharmacy. The DRPs in our study are as follows (Attachment 12):

- hypoglycemia,
- no documented BG,
- insulin-related indurations,
- need for additional BG tests,
- not administering insulin as prescribed
- Others (e.g.patient does not have BG records or diary or has only insufficient BG records).

It was initially planned to document DRPs at every pharmaceutical care visit, but due to the repetitive nature of DRPs and time-consuming documentation, pharmacists chose to record DRPs at one visit only. The goal of documenting the DRPs on a separate form (Attachment 12) was to define the type and rate of the most common problems in adolescents with T1DM, and not to assess the effect of the pharmaceutical care

intervention, which is done through the development and implementation of pharmaceutical care plans.

3.3.6. Adherence to Pediatric Guidelines

Adherence with selected pediatric diabetes guidelines was assessed using 12 selected items, in accordance with ISPAD 2009 and DDG 2010 guidelines (ISPAD Clinical Practice Consensus Guidelines 2009, DDG 2010) (Attachment 13). The following items were selected.

1) Individualized school plan.
2) SMBG performed at least four times daily.
3) Achievement of a target HbA1c of <7.5 %.
4) HbA1c testing performed four times per year.
5) Annual examination by ophthalmologist.
6) Annual screening for nephropathy.
7) Blood pressure checks performed every 3 months.
8) Lipid screening conducted every 2 years.
9) Annual neuropathy screening in patients with poor glycemic control.
10) Immunization, especially influenza and pneumococcal vaccination.
11) Sick day management protocol.
12) Testing of urinary or blood ketones.

To avoid overburdening pharmacists and patients with excessive documentation, adherence with guidelines was assessed at least once during the study; pharmacists could choose one random pharmaceutical care visit during which to perform the assessment. The items were divided into prevention of acute complications (items 1, 2, 10–12 from the above list) and prevention of long-term complications (items 3–9). In

this way, pharmacists could tick the box if the item was adhered to and note the date when the check was performed (Attachment 13). This document served as a basis for pharmacists to check with the patients if important guidelines have been adhered to by the diabetes healthcare team and the patients. For example:

- School plan: an individual plan should be created for the patient to give to their teachers, and contain information for the school about insulin dosage and frequency of use, timing of SMBG and timing of meals, and actions to correct hypo- and hyperglycemia (DDG 2010; ADA, Diabetes Care 2008).

- SMBG: to be performed at least four times daily to provide immediate documentation of hyperglycemia and hypoglycemia, and to allow implementation of optical strategies to treat and minimize out-of-range glucose values (Rewers et al. 2009, ISPAD 2009), as the frequency of SMBG is associated with improved HbA1c (Haller et al. 2004).

- Sick day management protocol: patients and their caregivers should be given clear and written guidance on the management of diabetes during illnesses to avoid the complications of ketoacidosis, dehydration, uncontrolled or symptomatic hyperglycemia and hypoglycemia (Brink et al. ISPAD 2009).

- Testing for urinary or blood ketones should be performed in the case of uncontrolled hyperglycemia, insulin deficiency, and during sick days (Rewers et al. 2009, Wolfsdorf et al. 2009, ISPAD 2009) as ketone testing can help avoid emergency room visits due to acute diabetes complications such as DKA (Wolfsdorf et al. 2009).

Using the tickboxes on the list (Attachment 13), pharmacists could interview the patients to determine whether the guidelines were adhered to. When correctly followed, these guidelines could potentially reduce the rate of preventable acute and late diabetes complications. If the guidelines were not being followed, pharmacists were advised to contact the diabetes team to discuss how to apply the guidelines in practice.

3.4. Data Analysis

Baseline data were analyzed and tested for any difference in patient characteristics between the intervention and control groups (i.e. null hypothesis [H0]: “there is no difference between the groups” vs. alternative hypothesis [H1]: “there is a difference between the groups”) using the Mann-Whitney test for quantitative variables and Chi - squared test (χ^2 test) for categorical variables, with continuity correction. In case of a small sample size, Fisher’s exact test was employed instead of the χ^2 test. The p-values were calculated and used to interpret the statistical significance of the differences between the groups.

All statistical analysis of data, including baseline characteristics and HbA1c data collected at baseline and after 3 and 6 months, was performed using the statistical software environment R, version 3.0.1 (R Foundation for Statistical Computing 2014). The Mann-Whitney test for quantitative (non-normally distributed) variables (i.e. the difference in HbA1c values at different timepoints were non-normally distributed or marginally normally distributed) to analyze primary and secondary outcomes, and the χ^2 or Fisher’s exact tests were used to analyze categorical variables in the secondary outcomes.

For the primary outcome analysis, the Mann-Whitney test was used, as the differences in HbA1c values at different time points were non-normally distributed or only marginally normally distributed. Potential country effects on the differences in HBA1c between time points were accounted for by linear regression analyses, performed using differences between two time points as outcome variables and the variables ‘group ’ (intervention/control) and ‘country’ (Bosnia/Germany) as explanatory variables. Wald tests based on this regression model were used to determine whether the variables ‘group’ or ‘country’ influenced the differences.

Secondary outcomes such as the WHO-5 Wellbeing Index, satisfaction with pharmaceutical care were further analyzed by linear models to test if baseline

covariates such as age, diabetes duration, sex, glucose, hypoglycemia, country and insulin delivery device influenced the results.

For the analysis of the secondary outcome “adherence with selected pediatric guidelines“, differences in adherence to guidelines (overall, prevention of long-term complications, and prevention of short-term complications) were tested in the groups “country”, “sex”, and “insulin delivery device”. However, as there were only few categories (few characteristic values) for the prevention of short- and long-term complications, a more adequate Chi squared test (χ^2 Test) was used to show trends.

4. Results

4.1. Study Protocol

4.1.1. Participant Recruitment and Flow

In total, 80 adolescent patients were screened for participation in the DIADEMA study (Figure 5). After assessment of inclusion and exclusion criteria by diabetes educators, 11 patients were excluded as they did not meet inclusion criteria (two patients had HbA1c ≤7.5% and one patient had mental disorder) and eight patients refused to participate for reasons of inconvenience and a lack of motivation; in total 69 patients were recruited into the study by the respective clinics from April 2012 to March 2013. Forty patients were randomized to receive pharmaceutical care (intervention group) and 29 patients were randomized receive usual care (control group). According to country, 26 patients were randomized to the intervention group and 20 to the control group in Bosnia-Herzegovina, whereas 14 were randomized to the intervention group and 9 to the control group in Germany. However, one patient in the control group in Germany was found to be erroneously enrolled, with HbA1c <7.5% (inclusion criterion is HbA1c ≥7.5%). This patient was subsequently excluded from the study and all data analyses. Therefore, 68 patients were included in the 3-month analysis and 65 patients completed the entire 6-month study (i.e. completed at least all six face-to-face pharmaceutical care appointments with the pharmacists) (Figure 4).

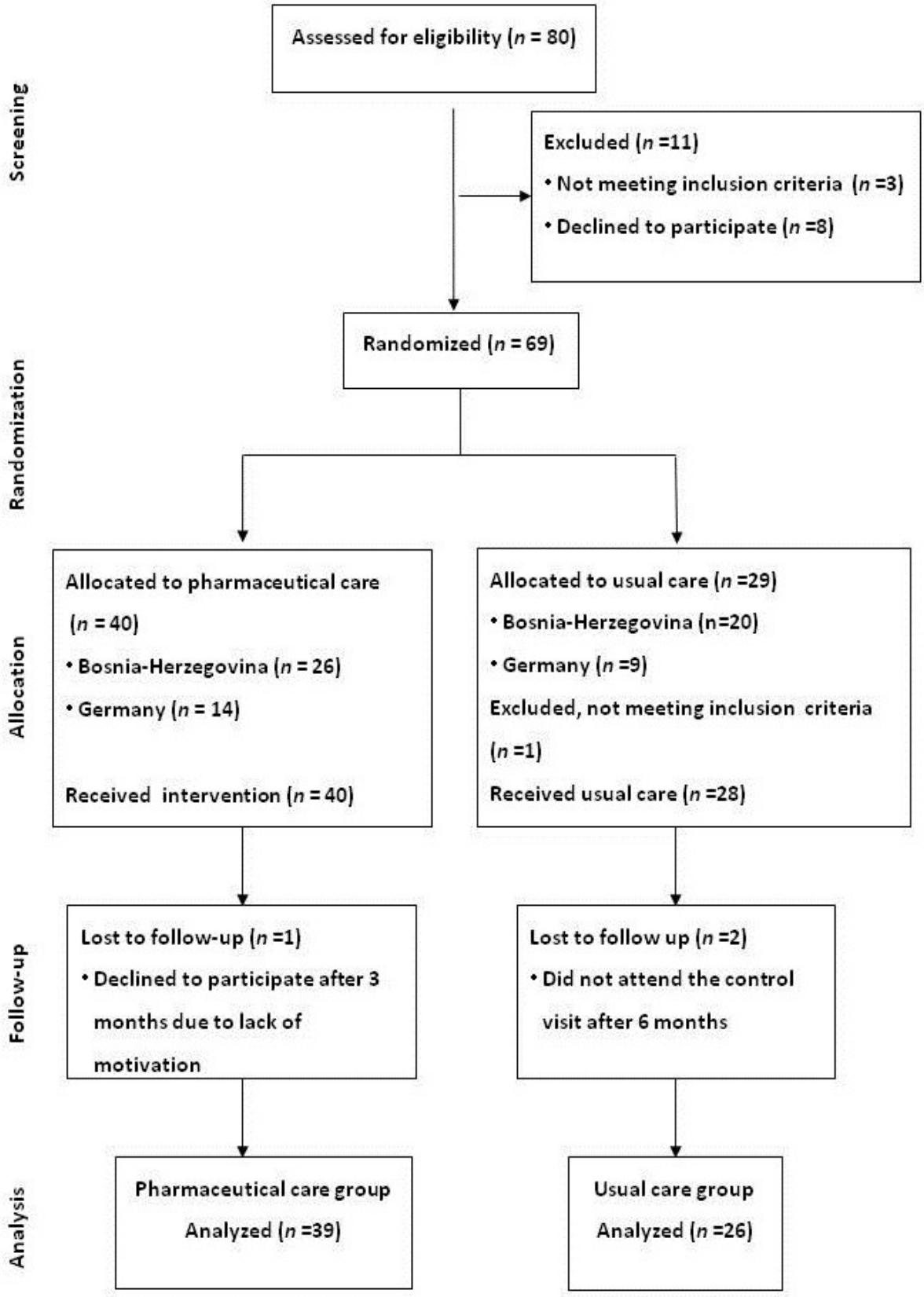


Figure 4: Patient flow of the DIADEMA study

4.1.2. Baseline Characteristics

At baseline, both groups had similar demographic and clinical characteristics (Table 9). The only significant difference was a higher mean high density lipoprotein (HDL) cholesterol levels in the intervention group than in the control group (65.2 mg/dL vs. 54.7 mg/dL, p = 0.001), although the HDL cholesterol values in both groups are considered clinically normal (>35mg/dL or 1.1 mmol/L) (ADA, Diabetes Care 2003).

Table 9: Baseline characteristics of study patients

Characteristics[a]	Intervention group	Control group	p-value
Patients (n)	40	28	
Bosnia-Herzegovina (n)	26	20	0.7685*
Germany (n)	14	8	0.7685*
Female gender (n) [%]	24 [60]	15 [54]	0.7807*
Mean age (years) [range]	14.5 [12–17]	14.9 [12–18]	0.2874**
Mean body mass index [range]	20.8 [14.5–27.5]	21.7 [17.1–29.1]	0.1864**
Mean duration of diabetes (years) [range]	5.9 [1–14]	6.8 [1–14]	0.2317*
1–3 co-morbid conditions (n) [%]	16 [40]	15 [54]	0.3751*[a]
Mean co-medications (n) [range]	1.1 [0–2]	1.3 [0–3]	0.6088*
Mean HbA1c (%)	9.4	9.4	0.5833*
>7.5% to <9% (n) [%]	19 [48]	14 [50]	0.8391*
≥9% (n) [%]	21 [53]	14 [50]	0.8391*
Mean BG (mg/dL) [range]	224.3 [30.6–555.0]	214.5 [28.8–470.3]	0.9404*
Mean self-reported home BG test per day (n)	4.2	4.0	0.885*
Mean insulin (IU/kg/day) [range]	53.7 [32–80]	55.4 [29–81]	0.6809**

Insulin pen, multiple daily injections (n) [%]	24 [60]	14 [50]	0.5692*
Insulin pump (n) [%]	16 [40]	14 [50]	0.5692*
Mean systolic BP (mmHg) [range]	118 [100–134]	121 [105–140]	0.2054**
Mean diastolic BP (mmHg) [range]	71 [51–98]	74 [46–100]	0.3263**
Mean total cholesterol (mg/dL) [range]	171.4 [104–282]	178.4 [108–344]	0.6092**
Mean LDL (mg/dL) [range]	104.2 [62–164]	108.4 [63–230]	0.8811**
Mean HDL (mg/dL) [range]	65.2 [16–124]	54.7 [18–139]	0.001*
Mean triglycerides (mg/dL) [range]	115.7 [25–1128]	132.8 [9–703]	0.6743*
Mean DKA episodes in the previous 6 months (n)	12	14	0.1411*
Mean severe hypoglycemia episodes in the previous 6 months (n)	8	6	1.000*

BG blood glucose, *BP* blood pressure, *HbA1c* glycated hemoglobin, *HDLC* high density lipoprotein, *LDLC* low density lipoprotein

[a] The number of co-morbid conditions was tested for dependency on 'group'

* Chi-square test; ** Mann-Whitney test; # Fisher's exact test

Patients in both groups had borderline total cholesterol levels (170–199 mg/dL) according to ADA and near-normal low-density lipoprotein (LDL) cholesterol levels (100–129 mg/dL). This correlation of suboptimal HbA1c with serum lipids has been described in other studies (Guy et al. 2009, Giuffrida et al. 2012). In the SEARCH for diabetes study, patients with suboptimal glycemic control also had elevated standard lipid levels (total cholesterol and LDL), as well as higher HDL cholesterol levels than healthy control subjects (Guy et al. 2009).

All study patients had a long diabetes duration, with an average of 5.9 years in the intervention group and 6.8 years in the control group. Use of the insulin pen and the insulin pump was similar between the two study groups. All participants had suboptimal glycemic control at baseline (HbA1c ≥7.5%). Patients were divided in two groups according to baseline HbA1c with similar distributions of HbA1c values between the study groups in terms of patients with suboptimal glycemic control (baseline HbA1c ≥7.5% to < 9%) or high risk glycemic control (baseline HbA1c ≥9 %) (Rewers et al. 2009, ISPAD 2009). Co-morbidities were reported in 36.8% of study participants, in 41% of patients in Bosnia-Herzegovina and 26% of patients in Germany. In Bosnia-Herzegovina, hypothyroidism was the most common co-morbidity and patients were stabilized on L-thyroxin (25–50 µg) before the study. In Germany, asthma, hay fever, and lactose intolerance were the most common. There were no significant between-group differences in the incidences of DKA and severe hypoglycemia in the 6 months prior to the study.

4.1.3. Pharmaceutical Care Intervention

In total 38 patients in the intervention group completed at least six and one patient completed five face-to-face pharmaceutical care visits (Table 8). The visits each lasted 60–90 minutes. During the 6-month study period, assessments were performed by collecting and documenting six CRFs per patient, including clinical patient data (e.g. sociodemographic, HbA1c, BG, blood pressure (BP), allergies, and past medical history) and by evaluating at least six patient BG records (from BG diaries). Six pharmaceutical care plans with identified drug therapy problems and at least one individual goal to be implemented by the next visit were developed. At each visit at least one Intervention to

resolve problems was documented and discussed with patients. Two written pharmaceutical care plans (visits 3 and 6) per patient were submitted and discussed with physicians and diabetes educators. Five follow-ups per patient evaluating progress in achieving individual goals and five reassessments for new problems were performed by the pharmacists.

4.2. Clinical Outcomes

4.2.1. Primary Outcome: HbA1c in the Intervention and Control groups

Relative to usual care, pharmaceutical care intervention successfully reduced HbA1c in adolescents with T1DM. Mean HbA1c decreased from 9.4% at baseline to 8.3% after 3 months and to 8.9% after 6 months in the intervention group, compared with an increase from 9.4% at baseline to 9.7% after 3 months and to 9.9% after 6 months in the control group (Figure 5 and Table 10).

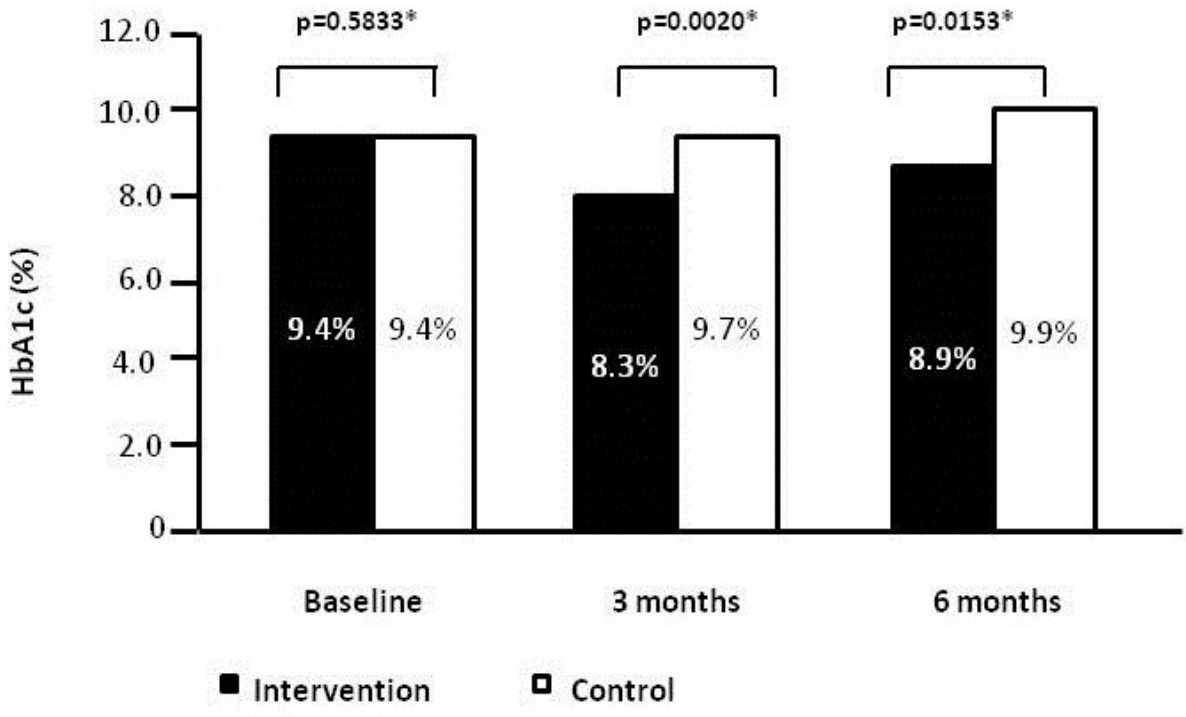


Figure 5: Mean HbA1c (%) values in the intervention (n=40, 40, 39) and the control (n=28,28,26) group at baseline, after 3 months and after 6 months of the study
HbA1c glycated hemoglobin; *Mann-Whitney test

Table 10: HbA1c outcomes (mean; %) [range] by study group and study country

Study population	Intervention group			Control group		
	Baseline (n = 40)	3 months (n = 39)	6 months (n = 39)	Baseline (n = 28)	3 months (n = 28)	6 months (n = 26)
All patients	9.4 [7.5–13.6]	8.3 [5.7–11.4]	8.9 [6.6–13.1]	9.4 [7.5–14.7]	9.7 [7.2–12.8]	9.9 [6.8–13.0]
p-values vs. control group	0.5833	0.0020	0.0153			
p-values vs.baseline*		0.00002	0.0075		0.00002	0.0075
Bosnia-Herzegovina	9.3 [7.5–13.6]	8.0 [5.7–11.2]	8.8 [6.6–13.1]	9.3 [7.5–14.7]	9.6 [7.2–12.8]	10.0 [7.7–13.0]
p-values vs. control group	0.4178	0.0037	0.0122			
p-values vs. baseline*		0.0001	0.0030		0.0001	0.0030
Germany	9.5 [7.5–12.2]	8.9 [7.2–11.4]	9.1 [7.1–12.5]	9.9 [7.7–12.9]	9.8 [7.8–12.8]	9.7 [6.8–11.7]
p-values vs. control group	0.5160	0.2450	0.4255			
p-values vs. baseline*		0.038	0.4281		0.038	0.4281

HbA1c glycated hemoglobin;

All p-values derived using the Mann-Whitney test;

*P values of difference in HbA_{1c} values in the intervention vs control relative to baseline

The difference in mean HbA1c between the timepoints “baseline” and “after 6 months” was −0.54% in the intervention and +0.32% in the control group; this change between the groups was significantly different, as testing whether these differences differ between the two groups leads to a p-value of p = 0.0075. This difference in HbA1c reduction between the two groups was even more significant after 3 months (mean difference in intervention group: −1.09% vs. 0.23% in control group; p = 0.00002) (Figure 6).

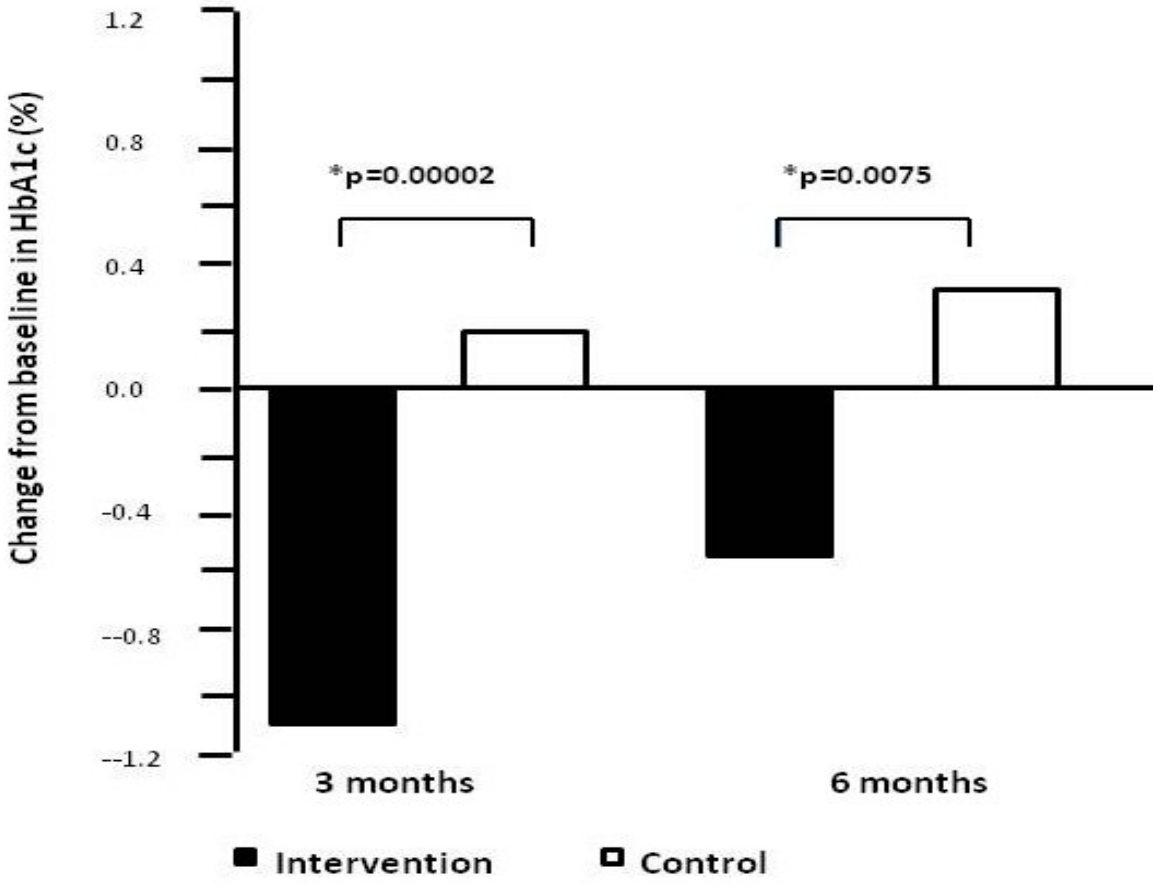


Figure 6: Mean HbA1c (%) values difference in the intervention (n= 40, 39) and control groups (n=28, 26) after 3 months vs baseline and after 6 months vs baseline

HbA1c glycated hemoglobin, *Mann-Whitney test

Figure 7 shows the distributions of the HbA1c levels as box plot for the intervention and control group at the three different time points. Box plots also show that the change in HbA1c was greater at 3 months than at 6 months in the intervention group.

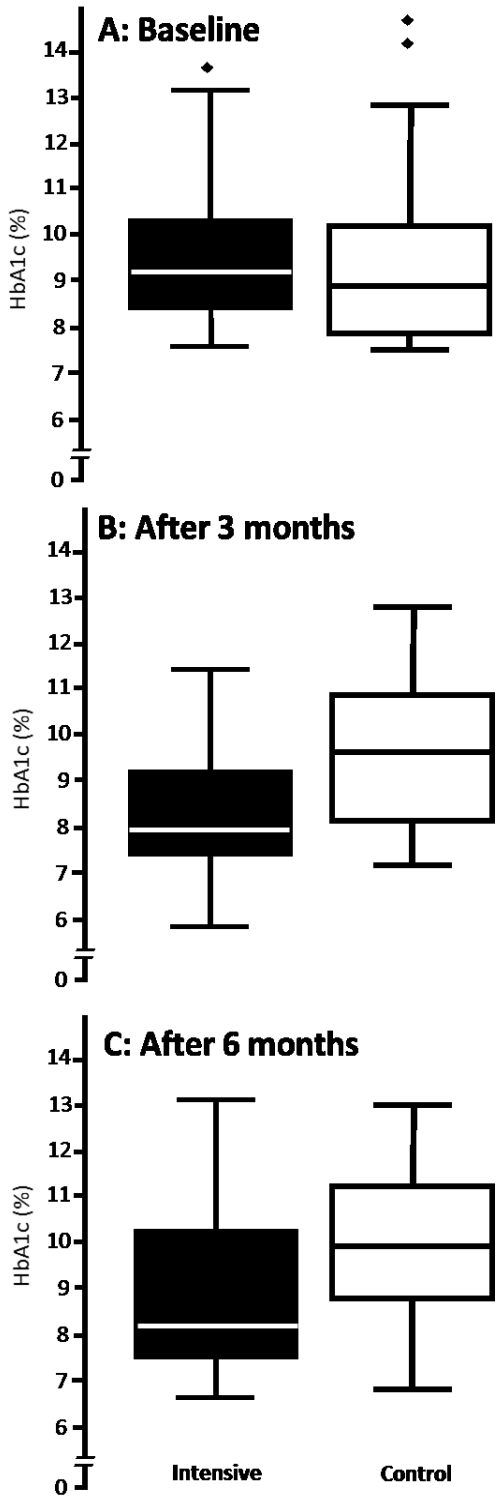


Figure 7: Distribution of HbA1c (%) values at three time points in the intervention and control groups. At baseline (A), after 3 months (B) and after 6 months (C) in the intervention (n = 40, 40, 39) and control (n = 28, 28, 26) groups. The middle line inside the box represents the median HbA1c (%). The central box represents the interquartile range (IQR) of variation of HbA1c (%) values.The "whiskers" above and below the box represent the minimum and maximum HbA1c (%) values. The black diamonds represent outliers with very low minimum and very high maximum HbA1c (%) values. Statistical difference of the data set is presented in Table 10. *HbA1c* glycated hemoglobin

The reductions in mean HbA1c were as expected larger in patients with high-risk glycemic control (baseline HbA1c ≥9%) than in patients with suboptimal glycemic control (baseline HbA1c >7.5 to <9%) after 3 (p = 0.050) and 6 months (p = 0.6978). However, these changes were not statistically significant, according to the Mann-Whitney test.

Linear regression models with the Wald test were used to analyze if the change in HbA1C was related to patient age. The test revealed negative values for the Wald statistics between baseline and 3 months (−0.318) and between baseline and 6 months (−1.099), indicating less HbA1c reduction with increasing age, although the trend is not statistically significant (p = 0.752 and p = 0.276, respectively).

A linear regression analysis was performed to test whether the HbA1c reduction is dependent on gender. A nominally significant dependence of HbA1c reduction on gender was seen between 3 months and baseline (p = 0.0323), meaning that the dependence is significant only if this statistical test is considered, disregarding multiple other statistical tests. HbA1c reduction was larger in female than in male patients, after 3 and after 6 months, respectively, as shown by positive values of the Wald statistic (Table 11).

Table 11: Gender dependence of the change in HbA1c

Comparison	p-value	Value of the test statistic
Difference between baseline and 3 months	0.0323	2.186
Difference between baseline and 6 months	0.461	0.742

HbA1c glycated hemoglobin

When analyzed by country, mean HbA1c improved to a significantly greater extent in the intervention group versus the control group at both 3 and 6 months, respectively, in Bosnia-Herzegovina (p = 0.0001 and p = 0.003), but only at 3 months in Germany (p = 0.038, p = 0.4281) (Table 10). This trend was also observed when the HbA1c results are presented by boxplot (Figure 9).

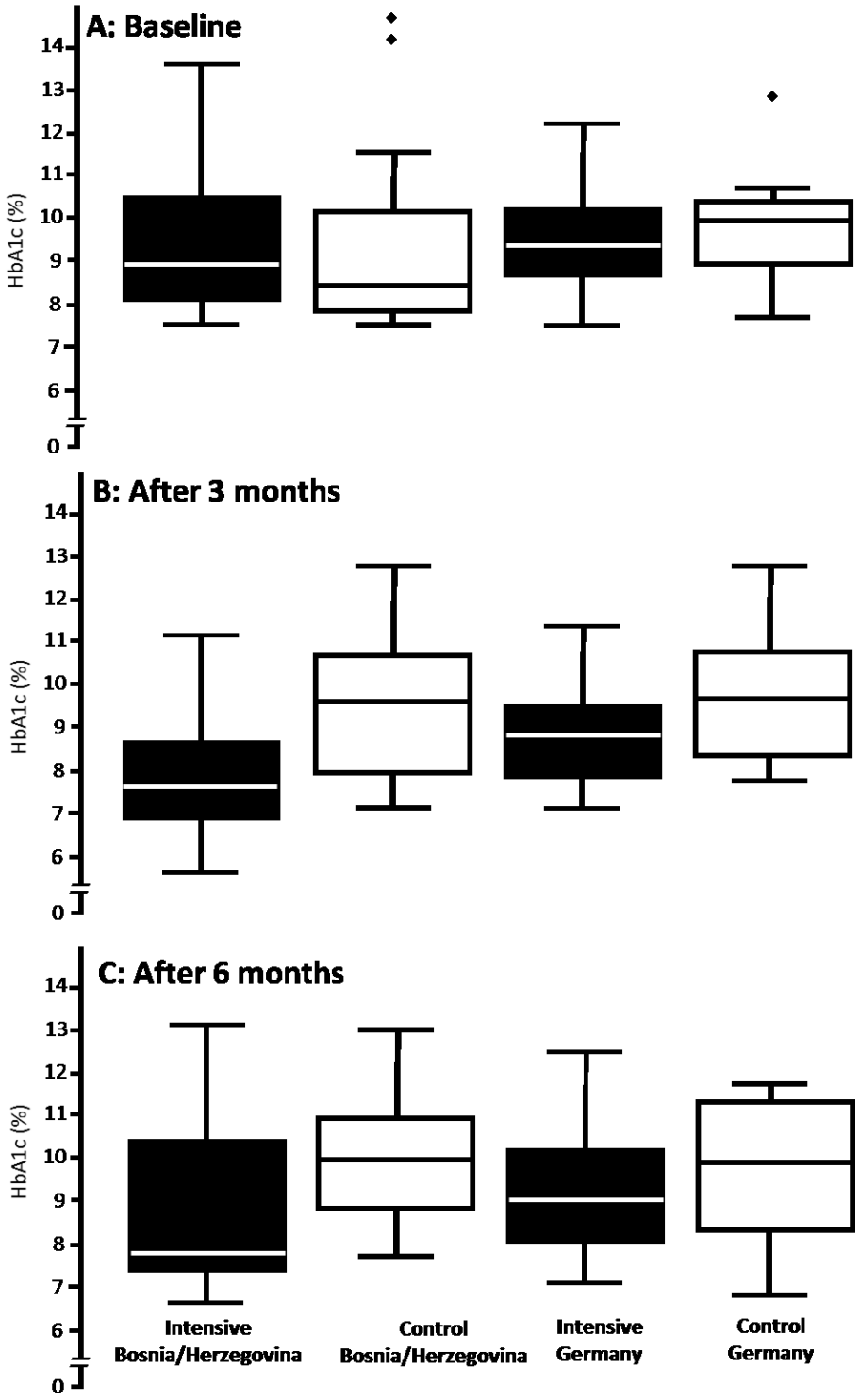


Figure 8: Distribution HbA1c (%) values at three time points in the intervention and control groups, stratified by country. At baseline (A), after 3 months (B) and after 6 months (C) in the intervention group in Bosnia (n = 26, 26, 26) and in Germany (n = 14, 14, 13) and in the control group in Bosnia (n =20, 20, 18) and in Germany (n = 8, 8, 8). The middle line inside the box represents the median HbA1c (%).The central box represents the interquartile range (IQR) of variation of HbA1c (%) values. The "whiskers" above and below the box represent the minimum and maximum HbA1c (%) values. The black diamonds represent outliers with very low minimum and very high maximum HbA1c (%) values. Statistical difference of the data set, stratified by country is presented in Table 10. *HbA1c* glycated hemoglobin

Because HbA1c outcomes differed between countries, potentially influencing the overall HbA1c result, linear regression was performed to adjust for the country effect. This analysis showed that the factor "country" had no significant effect on the differences in HbA1c values between baseline and 3 months (p = 0.2750) and between baseline and 6 months (p = 0.5879). Only the factor "group" (i.e. intervention or control) significantly influenced these differences, both at 3 months (p = 0.0000285) and at 6 months (p = 0.0078).

4.2.2. Long-Term Effect on HbA1c

Even though it was not a part of our original study protocol, HbA1c was measured after 12 months to test if the pharmaceutical care intervention resulted in a sustainable, long-term reduction of HbA1c. One year after the beginning of the DIADEMA study, mean total HbA1c was 8.6% in the intervention group compared to 9.5% in the control group, showing statistically significant result (p = 0.0183, Mann-Whitney test). (Table 12). After 1 year, the overall difference in HbA1c between the study groups was 0.9%.

Table 12: HbA1c outcomes (%) [range] after 12 months

Study population	Intervention group	Control group	p-value
All patients	8.6 [6.5–10.9]	9.5 [5.7–12.1]	0.0184
Bosnia-Herzegovina	8.5 [6.5–10.9]	9.5 [5.7–12.1]	0.0235
Germany	8.8 [7.4–10.6]	9.6 [7.3–12.9]	0.6272

HbA1c glycated hemoglobin

4.2.3. Post hoc Power Calculation

A post hoc power analysis of all subjects performed after the study for the comparison of the HbA1c reduction after six months between the intervention and the control group, using GPower 3.1 (Faul et al. 2007) and a nominal significance level alpha equal to 5% revealed a statistical power of 81.90%.

4.3. Secondary Outcomes

4.3.1. Severe Hypoglycemic Events (Both Groups)

The total number of severe hypoglycemic events recorded by diabetes educators was quantified using multiple sources such as patient medical records, hospitalizations due to severe hypoglycemia, BG records, and glucometer records. The majority of the patients, 82.5% in the intervention group and 82.1% and 96.4% in the control group, did not experience severe hypoglycemia events 6 months before or during the study respectively. In Bosnia-Herzegovina, six intervention group patients and five control group patients experienced episodes of severe hypoglycemia; in Germany, one intervention group patient and no control group patients experienced severe hypoglycemia during the study. A graphical representation of severe hypoglycemia events is presented in Figure 9.

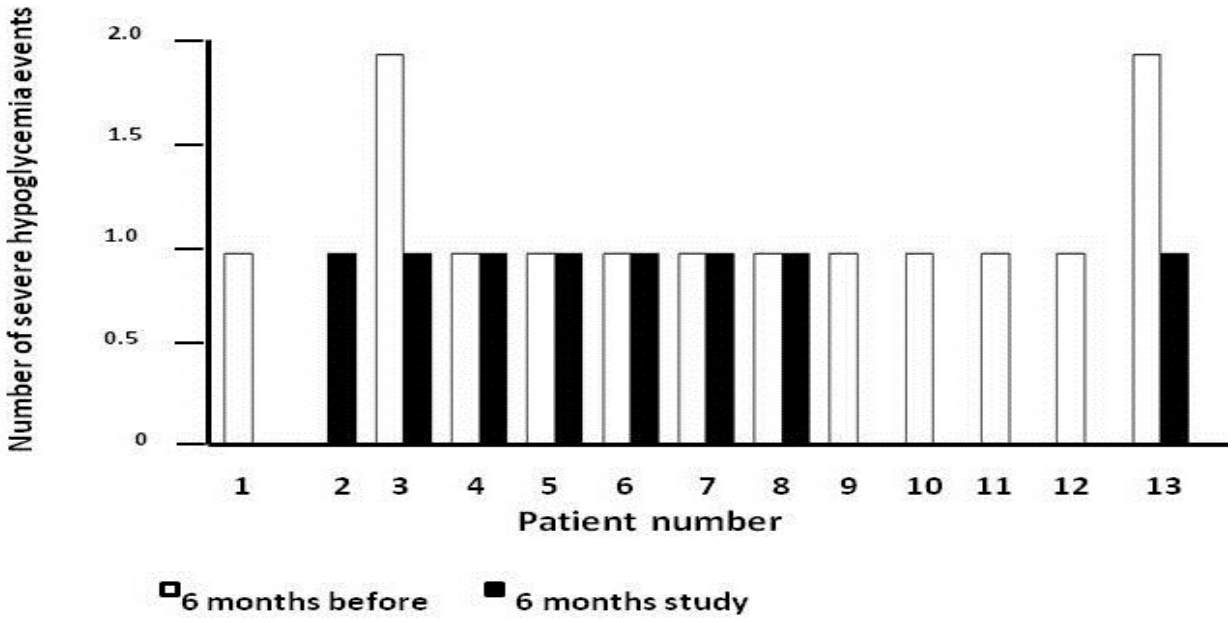


Figure 9: Number of severe hypoglycemia events of each patient in the intervention (n=40) and control groups (n=28) 6 months before the study and 6 months during the study .

There were no significant differences between the two groups in the in the distribution of severe hypoglycemic events during the study ($p = 0.1276$) or in the 6 months prior to the study ($p = 1$) (Table 13). There were only few occurrences of severe hypoglycemia. During the study, one severe hypoglycemic event was reported in 7 of 40 patients in the

intervention group and in 1 of 28 patients in the control group. Six months prior to the study, one event was reported in 6 and 4 patients in the intervention and control groups, respectively, while two events were reported in one patient in each group.

Table 13: Number of severe hypoglycemia events

Time period	Intervention group (n = 40)	Control group (n = 28)	p-value*
In the 6 months prior to the study	8	6	1
During the 6-month study	7	1	0.1276

* Fisher's exact test

4.3.2. Non-Severe Hypoglycemic Events (Intervention Group)

The number of non-severe hypoglycemic events recorded by diabetes educators per month did not change significantly over time. In the month prior to the study, 251 events were reported, with 268 at month 3 (p = 0.8157) and 184 at month 6 (p = 0.1787) (Table 14). This was an important endpoint, as HbA1c reduction was achieved without an increase in non-severe hypoglycemia. In fact, the number of non-severe hypoglycemia at month 6 was numerically lower (although not statistically significant; p = 0.0562) than at baseline.

Table 14: Number of non-severe hypoglycemia events

Time point	Intervention group (n = 40)	p-value*
Baseline	251	0.8157
Month 3	268	0.1787
Month 6	184	0.0563

* Mann-Whitney test

About half of the intervention patients (~50%) did not experience non-severe hypoglycemia at any time (baseline, 3 months, and 6 months). A graphical representation of non-severe hypoglycemia events in patients who experienced such events over the same time periods is presented in Figure 10.

The average number of non-severe hypoglycemia events per patient per month was 13.2 at baseline (assessed over the month prior to the study), 13.4 at month 3, and 10.2 at month 6 of the study respectively. There was one large outlier (Patient Nr.10) in Germany with extremely large numbers of 60 non-severe hypoglycemia episodes at baseline and after 3 months. This number was reduced to 8 episodes after 6 months of pharmaceutical care (Figure 10).

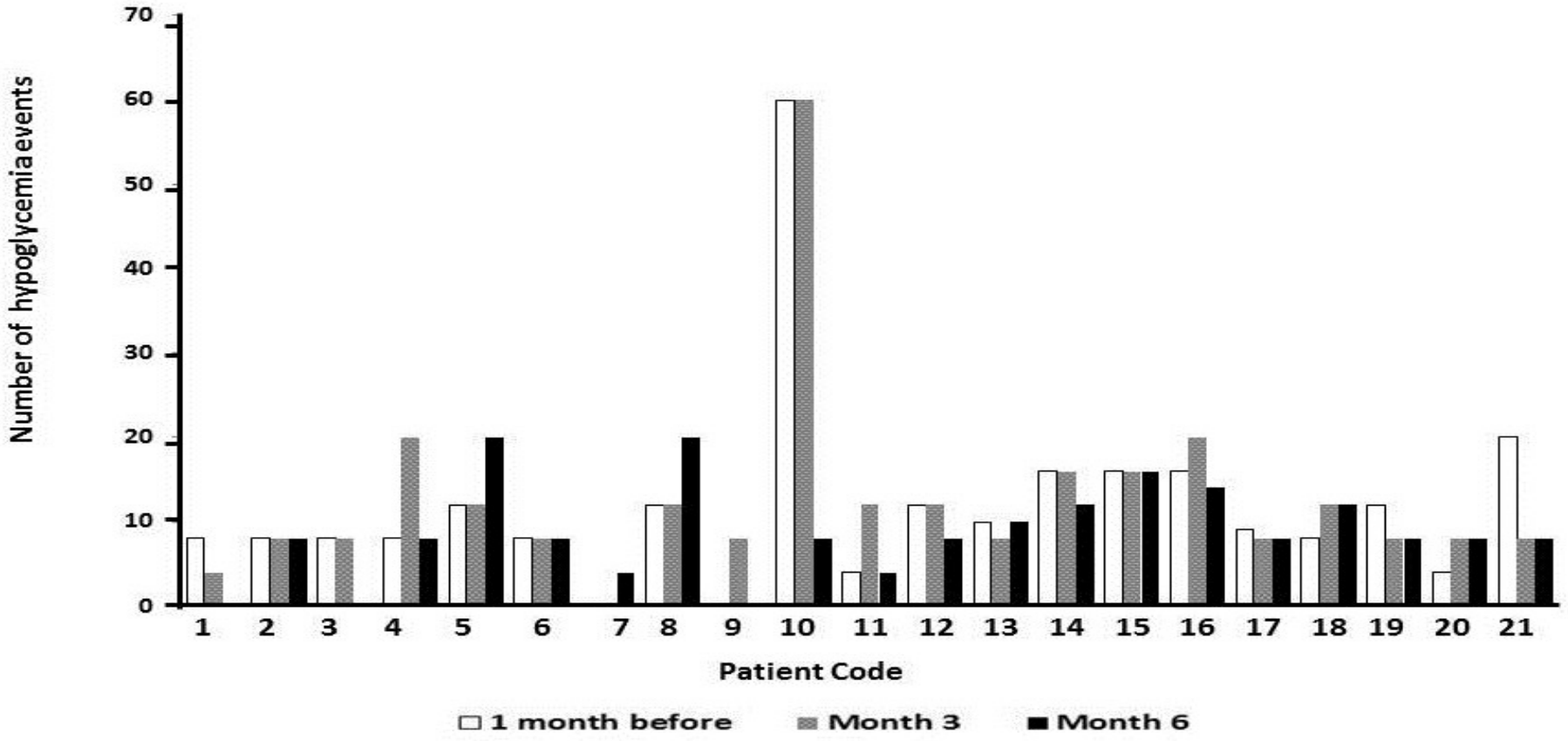


Figure 10: Number of non-severe hypoglycemia events in patients in the intervention group (n=40) 1 month before the study, at month 3 (n=40) and at month 6 of the study (n=39).

4.3.3. Wellbeing Index (WHO-5) (Intervention Group)

Quality of life was recorded by pharmacists using the Wellbeing Index (WHO-5) at the first pharmaceutical care visit (baseline), after 3 months, and after 6 months. A score below 13 points or 50% is indicative of low mood and a score below 7 points or 28% is indicative of likely depression (WHO-5 1998). In the intervention group, the mean baseline wellbeing score was 52.8% (range 16–84%) (Table 15); however, 45% of the patients had a score below 50% and 13% had a score below 28%. Wellbeing scores improved significantly to 59.2% (range 24–100%) after 3 months ($p = 0.0002$) and to 63.3% (range 24–96%) after 6 months ($p = 0.00002$). After 3 months, 33% of the patients had a score <50% and 3% had a score <28%. After 6 months, the scores improved further to 26% of patients with a score <50% and to 3% with a score <28%. Moreover, the change from baseline in wellbeing after 6 months was >10%, which is regarded as clinically relevant (WHO-5 1998).

Table 15: WHO-5 Wellbeing Index in the intervention group

Parameter	Baseline	3 months	6 months
Raw score	13.21	14.80	15.82
%	52.8	59.2	63.3
Change from baseline (%)		+6.4	+10.5
p-value*		0.0002	0.00002

* Mann-Whitney test

Using linear regression analysis, the baseline factors were tested for any influence on the change in WHO-5 scores between baseline and 3 months and between baseline and 6 months. Linear regression revealed that baseline covariates such as country ($p = 0.3922$; $p = 0.9563$), age ($p = 0.509$; $p = 0.7033$), insulin delivery device ($p = 0.1427$; $p = 0.7169$), glucose ($p = 0.9923$; $p = 0.2442$), duration of T1DM ($p = 0.8921$; $p = 0.9850$), other medication used ($p = 0.6042$; $p = 0.4558$), co-morbid conditions ($p = 0.3195$; $p = 0.4276$), hypoglycemia ($p = 0.7933$; $p = 0.2337$), severe hypoglycemia ($p = 1$; $p =$

0.6718), DKA (p = 0.2874; p = 0.471) at 3 and 6 months, respectively, did not influence improvements in wellbeing scores.

4.3.4. Satisfaction with Pharmaceutical Care (Intervention Group)

A 7-item questionnaire was used by pharmacists to assess patient satisfaction with pharmaceutical care at visits 3 and 6 (i.e. after 3 and 6 months). Patient satisfaction (maximum possible score 35) was rated high, with mean total scores of 29.9 (range 12–35) and 30.8 (range 19–35) after 3 and after 6 months, respectively.

The corresponding percentages of patient satisfaction were 85.6% after 3 and 87.9% after 6 months, revealing predominantly positive results and high satisfaction at both time points.

The satisfaction scores after 3 and after 6 months were compared using a two-tailed Mann-Whitney test to examine whether satisfaction with pharmaceutical care changed over time. The test revealed that satisfaction scores did not change significantly between months 3 and 6 (p = 0.1164) (Table 16). The last question of the pharmaceutical care questionnaire: ”Would the service pharmaceutical care help improve your blood glucose levels persistently if they were offered, for example in a public pharmacy or by a pharmacist in the hospital?” (Attachment 10) was rated high by the majority of patients (rated 4 or 5 out of a possible 5).

Table 16: Patient satisfaction with pharmaceutical care

Parameter	3 months	6 months	p-value*
Total score (range)	29.9 (12–35)	30.8 (19–35)	0.1164
Satisfaction (%)	85.6	87.9	

* Two-tailed Mann-Whitney test

Using linear regression analysis, baseline factors were tested for any significant influence on the patient satisfaction after 3 months and 6 months. The linear regression analysis showed that none of the baseline factors such as country (p=0.75; p = 1; p=0.2941), age (p = 0.5753;p = 0.5026; p = 0.6759), T1DM duration (p = 0.2621; p = 0.4827; p =0.7917), insulin delivery (p = 0.4023; p = 0.6602; p=0.8526), glucose (p =

0.7414; p = 0.0711; p=0.4198), or hypoglycemia (p = 0.5199; p = 0.4652; p=0.8611) significantly influenced the level of satisfaction after 3 and 6 months and the difference between 3 and 6 months, respectively.

4.3.5. Drug-Related Problems

DRPs recorded by pharmacists during one random pharmaceutical care visit were evaluated to define the type and rate of the most common problems in adolescents with T1DM. The majority of pharmacists (80%) recorded DRPs at the last pharmaceutical care visit, whereas the other remaining 20% recorded DRPs at earlier visits. (PhC visits 1-5)

The pharmacists' interventions regarding DRPs were not documented on this form, but rather in the pharmaceutical care plan, as the goal was to identify and name the most common DRPs.

Several DRPs were identified by the pharmacists (Table 17). All 39 patients in the intervention group experienced at least one DRP. A total of 103 DRPs were identified, with a mean of 2.6 DRPs per patient. The most common DRPs originated from the underlying T1DM: hyperglycemia (98%), hypoglycemia (51%), no or insufficiently documented BG (51%), side effect of insulin (indurations) (31%), additional BG tests needed (18%), and not administering insulin as prescribed (15%). The percentage distribution of identified DRPs is depicted in Figure 11.

Table 17: Overview of drug-related problems

Identifier	Problem	No. of patients
DRPD1	Elevated BG levels (hyperglycemia)	38
DRPD2	Hypoglycemia	20
DRPD3	Additional BG measurements required	7
DRPD4	Adverse effect (insulin)	12
DRPD5	More effective dosage form available (insulin)	0
DRPD6	Patient does not want to take insulin	6
DRPD7	Patient does not understand the instructions	0
DRPD8	Patient has no / insufficient BG diary	20

BG blood glucose

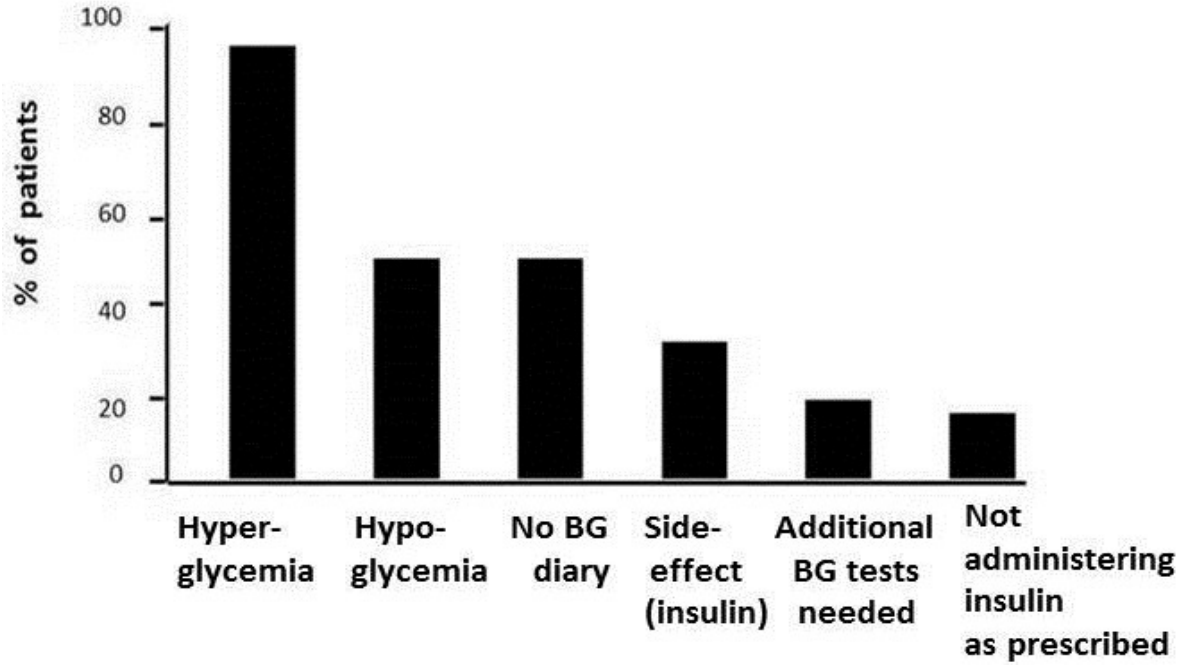


Figure 11: Percentage distribution of drug-related problems in the intervention group (n=39) at one pharmaceutical care visit
***BG* blood glucose**

4.3.6. Adherence to Pediatric Guidelines

Adherence to 12 carefully selected items taken from current pediatric guidelines (ISPAD 2009, DDG 2010) was evaluated by the questionnaire "Adherence to pediatric guidelines" (Attachment 13). Guideline adherence was recorded by pharmacists at one random pharmaceutical care visit. The majority of pharmacists (72%) assessed guideline adherence at PhC visit 1, 8 % at visit 3, and 20% at visit 6.Adherence to the 12 items from pediatric guidelines was 57%. Items for the prevention of long-term diabetic complications (e.g. retinopathy, nephropathy) were associated with a satisfactory adherence rate of 78%; items for the prevention of short-term complications (e.g. DKA) had a poor adherence rate of 26%. Adherence rate to items for the prevention of short-term complications was 10% for blood or urinary ketone testing, 10% for sick day management, and 8% for individualized school plan. These items were identified as areas for improvement and were discussed with diabetologists and diabetes educators. An overview of guideline adherence is shown in Table 18.

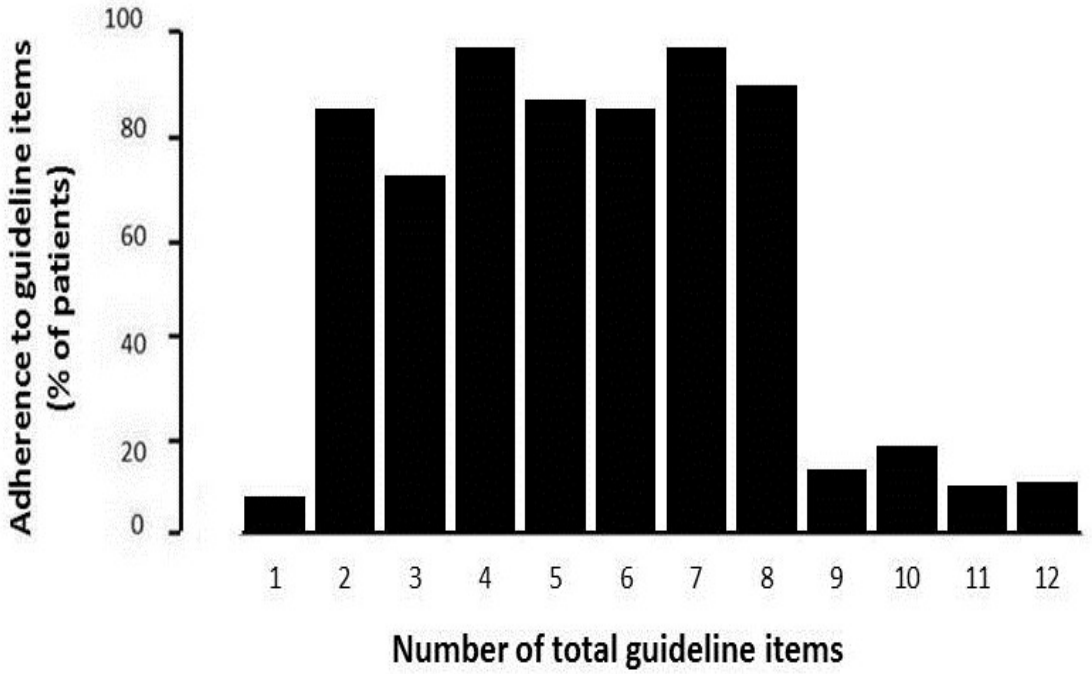
Table 18: Overview of patient adherence to selected pediatric guidelines (n = 39) (Attachment 13)

Item no.	Guideline	No. of patients
Prevention of long-term complications		
3	Achievement of target HbA1c (<7.5%)	28
4	HbA1c tested four times per year	39
5	Annual ophthalmologist examination	33
6	Annual screening for nephropathy	34
7	Blood pressure checked every 3 months	39
8	Lipids screened every 2 years	36
9	Annual neuropathy screening in patients with poor glycemic control	5
Prevention of short-term complications		
1	Individualized school plan	3
2	SMBG performed at least four times daily	34
10	Immunization, especially influenza and pneumococcal vaccination	7
11	Sick day management protocol	4
12	Urinary or blood ketones testing	4

HbA1c glycated hemoglobin, *SMBG* self-monitoring of blood glucose

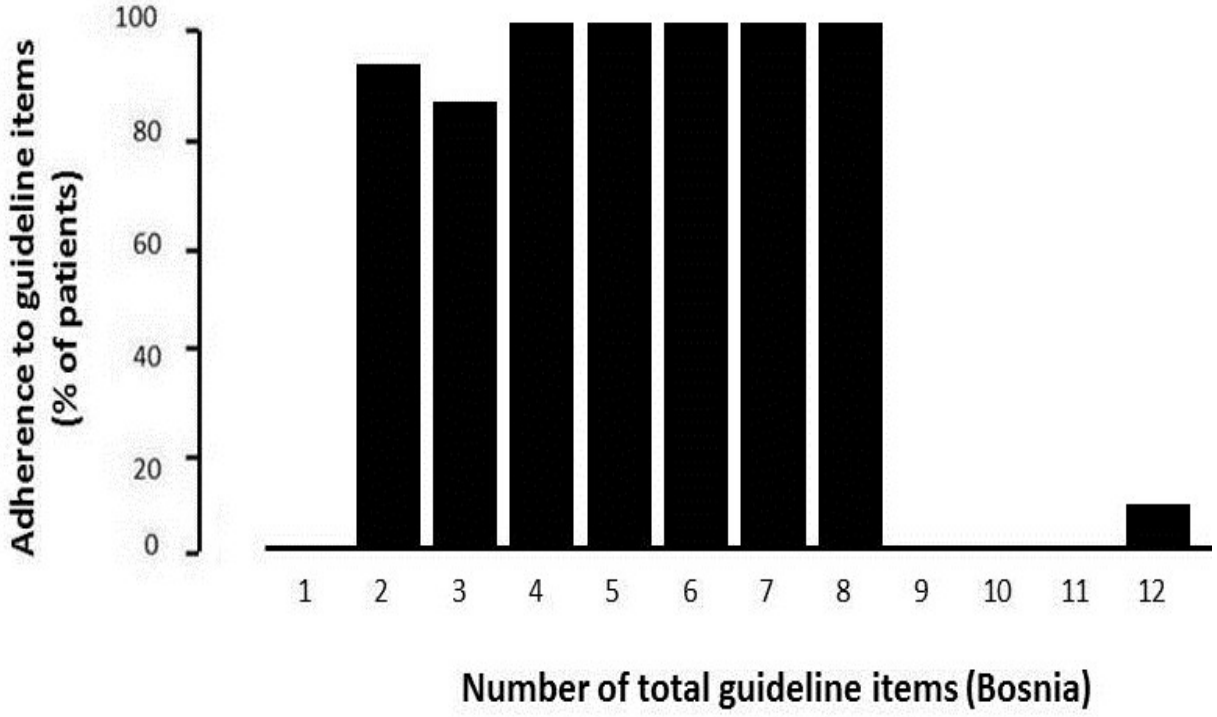
Figure 12 illustrates guideline adherence. Most (70% or more) of the patients showed a satisfactory adherence to guideline items Nr. 2–8 , whereas guideline items Nr. 1, 9–12 were less adhered to (all <18%). In Bosnia Herzegovina items for the prevention of long-term diabetic complications had a better adherence (all >85% adherence, except for neuropathy screening) (Figure 13), however items for the prevention of short -term diabetic complications, items 1, 10 and 11 (e.g. school plan, immunization especially influenza and pneumococcal, sick day protocol) where not adhered to at all. In Germany, all guidelines were adhered to, however some items for the prevention of long-term diabetic complications to a lesser extent then in Bosnia (Items 3 and 5: target HbA1c <7.5% and ophthalmology exam), although unlike in Bosnia items for the

prevention of short-term diabetic complications such as items nr. 1, 10 and 11 showed certain adherence rate (Figure 14).



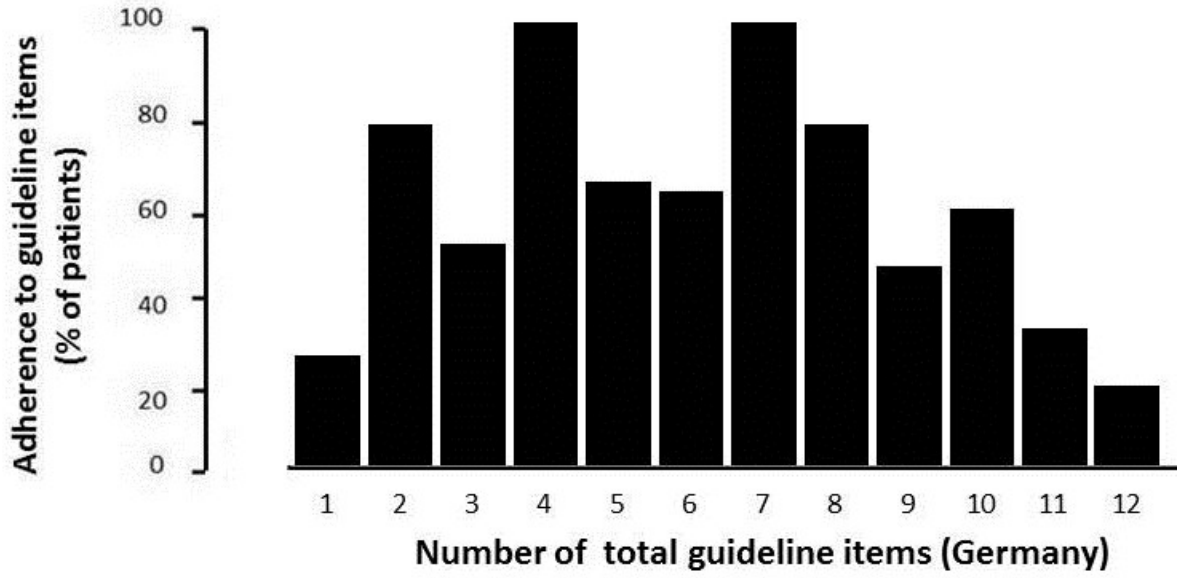
1) Individualized school plan.
2) SMBG performed at least four times daily.
3) Achievement of a target HbA1c of <7.5 %.
4) HbA1c testing performed four times per year.
5) Annual examination by ophthalmologist.
6) Annual screening for nephropathy.
7) Blood pressure checks performed every 3 months.
8) Lipid screening conducted every 2 years.
9) Annual neuropathy screening in patients with poor glycemic control.
10) Immunization, especially influenza and pneumococcal vaccination.
11) Sick day management protocol.
12) Testing of urinary or blood ketones.

Figure 12: Percentage distribution of adherence to all 12 selected pediatric guidelines in the intervention group (n= 39) in both countries at one pharmaceutical care visit



2) SMBG performed at least four times daily.
3) Achievement of a target HbA1c of <7.5 %.
4) HbA1c testing performed four times per year.
5) Annual examination by ophthalmologist.
6) Annual screening for nephropathy.
7) Blood pressure checks performed every 3 months.
8) Lipid screening conducted every 2 years.
12) Testing of urinary or blood ketones.

Figure 13: Percentage distribution of adherence to all 12 selected pediatric guidelines in the intervention patients (n= 26) in Bosnia-Herzegovina at one pharmaceutical care visit



1) Individualized school plan.
2) SMBG performed at least four times daily.
3) Achievement of a target HbA1c of <7.5 %.
4) HbA1c testing performed four times per year.
5) Annual examination by ophthalmologist.
6) Annual screening for nephropathy.
7) Blood pressure checks performed every 3 months.
8) Lipid screening conducted every 2 years.
9) Annual neuropathy screening in patients with poor glycemic control.
10) Immunization, especially influenza and pneumococcal vaccination.
11) Sick day management protocol.
12) Testing of urinary or blood ketones.

Figure 14: Percentage distribution of adherence to all 12 selected pediatric guidelines in the intervention patients (n= 13) in Germany at one pharmaceutical care visit

In order to test whether the covariates “country”, “groups”, ”sex“, and “insulin delivery device“ had an influence on the adherence score, these factors were analyzed with χ^2 test for trends. A linear model was used to test the other variable “diabetes duration”.

The results showed that the covariate “country” was the only important correlate, as it influenced both the prevention of short-term complications (p = 0.003) and prevention of long-term complications (p = 0.002), but not overall adherence (p = 0.8874). Hence, the adherence in Germany (37%) to guideline items of prevention of short-term complications was greater than in Bosnia-Herzegovina (20%), whereas adherence in Bosnia-Herzegovina to the prevention of long-term complications was more prominent (84% vs. 68% in Germany). Other covariates, such as “sex“(p = 0.4306, p = 0.3132, p = 0.0475), “insulin delivery device” (p = 0.0239, p = 0.3158, p = 0.1969), and “diabetes duration” (p = 0.1872, p = 0.1401, p = 0.5592) did not influence overall adherence to guidelines or adherence to long-term prevention and short-term prevention, respectively.

5. Discussion

5.1. Study Protocol

5.1.1. Participants and Pharmaceutical Care Visits

Implementation of a structured pharmaceutical care was not easily achieved. Because our study was conducted in adolescents (aged 12–18 years), it was a challenge to recruit patients, and even more so to motivate them for repeated visits and to continue with the pharmaceutical care, due to decreasing motivation inherent to their developmental stage (Borus et al. 2010, Hamilton et al. 2002). The study pharmacists had to apply their interpersonal communication skills and, in many instances, give repeated calls and reminders to parents and patients to attend the monthly pharmaceutical care visits. Some patients have a generally lower level of healthcare, with less education and healthcare-related knowledge than other patients, and found it particularly difficult to accept the benefits of additional visits with the pharmacists. It was up to the pharmacists, in addition to imparting education and developing the pharmaceutical care plans, to be a partner of sorts to the adolescents in this study, to demonstrate compassion, understanding and, above all, to convince them of the benefit of pharmaceutical care without judgment. Many of the study adolescents did not appear to care about their future, and this apathy created a difficult challenge for many of the study pharmacists.

These and other concerns (e.g. insecurities regarding provision of PhC) were regularly addressed during the DIADEMA team meetings (held every two months), where pharmacists were supported by interaction with other members of the study team (e.g. diabetologists and other study pharmacists) to gain confidence in addressing the challenges they faced. Another difficulty was finding a sufficient number of eligible patients. Only 80 patients in total from both countries were identified as potential study candidates. Out of these, three patients did not match inclusion criteria and eight patients declined to participate for reasons of disinterest and inconvenience of the required additional visits. Therefore, only a small number of patients were recruited.

One patient was mistakenly recruited (despite a baseline HbA1c% of <7.5) and was subsequently excluded, giving a total of 68 patients. One patient from the intervention group declined to participate after 3 months due to a misunderstanding with the study pharmacist, and two patients from the control group were lost to follow-up after 6 months, possibly due to disinterest as no emergency visits or hospitalizations occurred at that time. Sixty-five patients completed the entire study period, 39 in the Intervention group and 26 in the usual care group.

The pharmaceutical care visits (in pharmacies in Germany or in the clinic in Bosnia-Herzegovina) took place in separate rooms specifically designated for confidential discussions between patients and pharmacists, so that the adolescents felt less observed and more confident. This may be the reason that, although the parents could participate in the pharmaceutical care visits, the vast majority of adolescent patients opted to be alone with the pharmacists. However, although the setting was private and optimized for conversation, the challenge of compliance in the adolescents soon became apparent. Pharmacists had to use different methods to convince the patients to attend the appointments, such as sending them reminder emails or text messages, and if no answer was received, to contact the parents, teachers, and/or the diabetes team, which were usually successful. If these strategies did not work, pharmacists would persist with proposing new appointment times that were suitable for the patients.

As a prerequisite for the pharmaceutical care visits, pharmacists had access to the patients' HbA1c data from the clinics, and patients had to bring their BG records (from their BG diaries) for the 7 days prior to the visits. Patients in the intervention group had to document their BG at least four times daily (i.e. fasting, after administering insulin, in response to insulin action peaks and troughs, and bedtime) (Rewers et al. 2009), preferably 5–6 times to include measurements 2 hours after meals or during or after sports. Based on data and evaluation of BG records, pharmacists assessed drug-related needs and identified problems (e.g. insulin non-adherence at school, dose adjustment for hyperglycemia or sport).

In reality, this was difficult to achieve, and in the DIADEMA study protocol, a written BG record of the previous 24 hours was also acceptable. Therefore many adolescents who were not fully compliant with recording BG measurements for the previous 7 days

provided BG records for the previous 24 hours. Pharmacists were advised not to be judgmental regarding the BG records but to use them as a tool for patient discussions as part of the pharmaceutical care plan, and for discussing problem-solving strategies in concert with the patient.

Pharmaceutical care intervention was standardized in both countries according to Cipolle (2004) and consisted of evaluation of BG records, assessment of drug-related needs and DRPs (e.g. insulin non-adherence at school, dose adjustment for hyperglycemia or sports). Individual pharmaceutical care plans were developed for each patient, which included problem-solving interventions and at least one measurable goal. Most of the study pharmacists were also pharmacy owners, with the responsibilities of maintaining their pharmacies, including drug and supply ordering. Some of the study pharmacists considered the intense patient monitoring and pharmaceutical care plans and study CRF documentation required to be “bothersome” and time consuming, and admitted that they could not easily accommodate pharmaceutical care in their daily work, due to enormous time constraints and a lack of financial compensation. It is worth noting that in both study countries, the traditional practice of pharmacists is focused primarily on distributing insulin, with diabetes educators imparting education on insulin and glucose monitoring. Nevertheless, most of the study pharmacists reported that they enjoyed their new “clinical” role and felt positive about the extraordinary co-operation with the clinics and diabetologists, which is not the norm in both countries.

5.2. Clinical Outcomes

5.2.1. Primary Outcome: HbA1c in the Intervention and Control Groups

The DIADEMA study showed that pharmaceutical care can add value to improve diabetes outcomes in T1DM adolescents with poor glycemic control, as demonstrated by HbA1c reductions without increases in the rate of either severe or non-severe hypoglycemia events. This finding was observed irrespective of study country, as the country covariate did not significantly influence the HbA1c outcome. However, studies in the T1DM adolescent population remain scarce. Our findings, in particular the HbA1c reduction, are in contrast to previous research conducted with pharmacists and

adolescents with T1DM. In a randomized, controlled, study conducted in France in 100 patients aged 8–17 years and pharmacists using telecare who downloaded and faxed glucometer data to the hospital without providing further education to the patients, no significant difference in mean HbA1c between the intervention and control groups were observed (Gay et al. 2006). This study confirmed the compliance challenge among adolescents, as only 33 out of 50 adolescents in the intervention group transmitted at least one fax (Gay et al. 2005). A small observational American study that assessed six patients, in which pharmacists directed a peer-support program, showed an increase in HbA1c, further supporting the challenge of reaching metabolic control during adolescence (Sims et al. 2011). However, an improvement in adherence to lifestyle modification and health perception was reported in this study (Sims et al. 2011). The lack of HbA1c reduction in these studies (Sims et al. 2011, Gay et al. 2005) may result from an absence of a structured pharmaceutical care, as defined in Standards of Practice (Cipolle et al. 2004), as the pharmacist interventions in these studies were not sufficient to improve patient outcomes in this specific population.

In our study, pharmacists assessed clinical data (e.g. HbA1c levels) and evaluated patient BG records. The pharmacists then developed pharmaceutical care plans with problem-solving interventions. These care plans served as a basis for communication with the patients and the physicians. The problem-solving interventions were devised in concert with the patients to define responsibilities (van Mill et al. 2004). Patients were empowered by the pharmacists to actively seek a solution for their drug-related needs. In this way, we actively involved patients in the pharmaceutical care process to improve adherence.

Furthermore, the pharmaceutical care plans were discussed and patient progress in achieving their individual goals was evaluated with physicians. Pharmacists submitted and faxed pharmaceutical care plans after visits 3 and 6 in addition to attending the regular DIADEMA meetings, held every two months, at which pharmaceutical care plans were discussed between pharmacists, physicians and diabetes educators. Immediate insulin dose changes were proposed to physicians by phone during patient visits and patients were advised to visit their diabetologists who could adjust the insulin dose.

Therefore, implementation of an appropriate, structured, and multidisciplinary pharmaceutical care plan along with patient empowerment appears to be crucial for the improved glycemic control observed in our study.

Two large studies with pharmaceutical care and a multidisciplinary approach have been conducted over 6 months in patients with T2DM. One of the studies was a randomized, controlled, parallel-group trial in 66 community pharmacies in Belgium (n = 288), which showed an improvement in HbA1c of 0.5% in the intervention group. Patients who had a medication change by physicians that was supported by pharmacists had an even better HbA1c reduction of 1.05% (Mehuys et al. 2010). The other study, conducted in Australia (n = 289) with 56 community pharmacies, reported a decrease in mean BG levels and a significant reduction in HbA1c of 0.97% in the intervention group (Krass et al. 2007). Thus, these studies with a 6-month duration reported an HbA1c reduction ranging from 0.5% to 1%, which is comparable to our findings. Our trial further supports the value of pharmacists in a multidisciplinary team to reduce disease burden in patients with T1DM.

Remarkably, in both countries, a greater HbA1c reduction was achieved after 3 rather than 6 months, possibly because of decreasing patient motivation. As mentioned above, pharmacists had to find different ways to retain patient motivation for the entire duration of the study, which was not an easy task. This finding supports those of previous studies (Borus et al. 2010, Sims et al. 2011, Frank et al. 2005) showing adherence challenges in adolescents, intrinsic to the developmental stage (Borus et al. 2010) and requires a longer follow-up with new approaches to sustain the initial improvement seen with pharmaceutical care. This was one of the reasons why we performed an analysis of HbA1c values after 12 months, and which was not part of the original study protocol. We were pleasantly surprised by the favorable HbA1c outcome of 8.6% in the intensive care group versus 9.5% in the control group (Table 12). This equated to an overall HbA1c difference of 0.9% between the groups (Mann-Whitney test $p = 0.0184$), which indicates that, even after the end of the study, study pharmacists maintained contact with the patients, and patients remained empowered and were able to continue to manage their T1DM with the support from the pharmacists.

Although HbA1c reduction was achieved in both countries, the effect was more prominent in Bosnia-Herzegovina, which may be due to the on-site presence of the clinical pharmacist, inevitably leading to more intensive and more profound contact between the patients, the pharmacist and the physicians. Furthermore, Bosnian patients have a lower baseline in terms of care, knowledge, and education due to the limited healthcare resources, as a result of overall difficulties with the current political and economic situation. Therefore, it seems natural that any patient-focused approach is likely to yield a substantial improvement. In addition, limited healthcare and overall resource shortage may have contributed to better acceptance and adherence of pharmaceutical care by the youths in Bosnia.

Another interesting observation from our study was that patients in the German control group demonstrated slight improvement in HbA1c (Table 10), thereby decreasing the effect of the pharmaceutical care intervention, known as the Hawthorne effect (McCarney et al. 2007). It is likely that patients in the control group in Germany were more extensively familiarized with clinical trial procedures than patients in Bosnia, where no ethical approval was required.

To facilitate participation in the DIADEMA study, 14 study pharmacists in Germany received intensive individual training before the study, on subjects including pharmaceutical care, T1DM pathophysiology and management, and GCP. During the study, pharmacists were trained in group sessions on the management of T1DM, using DIADEMA patients as case studies. However, despite intensive training, German pharmacists showed varying competence in pharmaceutical care, especially those who were older, who did not have clinical pharmacy and pharmaceutical care as part of their pharmacy studies curriculum. These pharmacists often felt insecure and not up to the task of delivering pharmaceutical care to the patients. They also showed concern about communication with the physicians. These facts may explain the less favorable outcomes seen in some participants in Germany.

5.3. Secondary Outcomes

5.3.1. Severe and Non-Severe Hypoglycemia

As stated previously, the goal of the study was to improve glycemic control in T1DM patients who had poor glycemic control, in order to minimize long-term microvascular and macrovascular complications (Rewers et al. 2009) without increasing the rates of severe and non-severe hypoglycemia. Many studies report an increased risk of hypoglycemia in association with an aggressive reduction of HbA1c (DCCT 1993, Nordfeldt et al. 1999, Mitrakou et al. 1991). The importance of not increasing the risk of hypoglycemia is emphasized by findings that severe hypoglycemia is a significant cause of morbidity and occasional mortality in young patients with T1DM (Nishimural et al. 2001, Sovik et al. 1999, Weston et al. 1999). Furthermore, nocturnal hypoglycemia is the suspected cause of death in the rare "dead in bed" phenomenon in young patients with T1DM (Gill et al. 2009). If left inadequately treated, even minor hypoglycemia can result in coma, convulsions and death (Cryer 2007), although it is controversial whether severe hypoglycemia causes lasting damage to cognitive function or dementia. Although the Diabetes Control and Complications Trial (DCCT 1993), with a long-term follow-up of over 20 years, did not prove a causal relationship between severe hypoglycemia and cognitive dysfunction (DCCT/EDIC 2007), several other trials report that severe hypoglycemia and recurrent episodes of hypoglycemia may cause permanent CNS changes and cognitive dysfunction in children (Strudwick et al. 2005, Hannonen et al. 2003) and dementia in elderly persons aged over 65 years (Whitmer et al. 2009). Thus, the impact of severe hypoglycemia on cognitive function appears to be age dependent.

Therefore, pharmacists in our study advised patients to closely monitor their insulin therapy in concert with the diabetes team, and encouraged and supervised patients to perform frequent BG monitoring to minimize the occurrence of hypoglycemia and hypoglycemia unawareness (Rewers et al. 2009). At each pharmaceutical care visit, pharmacists addressed the hypoglycemia issue by collecting subjective patient information with open questions such as: "How have things been going with hypoglycemia since your last visit?" and "Tell me about the last hypoglycemia episode

you had". As before, patient empowerment played a key role in addressing the prevention of hypoglycemia. Patients were questioned by the pharmacists to demonstrate their understanding of the timing of insulin administration, insulin action profiles, the impact of food (with an exact meal plan, including snacks) on hypoglycemia, and that sports and alcohol can cause hypoglycemia (Cryer et al. 2003).

The patients and their parents in our study had a major fear of hypoglycemia. Pharmacists had to educate patients that, with proper insulin dosing and frequent BG monitoring, hypoglycemia can be avoided; the pharmacists also provided reassurance to patients and their parents, because a fear of hypoglycemia posed a barrier to achieving glycemic control.

Pharmacists discussed the HbA1c targets individually with each patient, raising these targets to above 7.5% in consultation with the physician (Rewers et al. 2009, ISPAD Guidelines 2009) if frequent severe or non-severe hypoglycemia was encountered.

In summary, the substantial HbA1c reduction of 1.1% after 3 months and of 0.5% after 6 months achieved in our study was not at the expense of increased hypoglycemia rates, as shown by the stable rates of severe hypoglycemia from the 6 months prior to the study to the 6-month duration of the study in both the intervention and the control groups. In addition, the rate of non-severe hypoglycemia in the intervention group did not increase from baseline after 3 or 6 months of the study.

5.3.2. Wellbeing Index (WHO-5) (Intervention Group)

Implementation of a structured pharmaceutical care by the pharmacists positively influenced the perception of wellbeing in the study adolescents, which is reflected as a better overall quality of life. The adolescents in our study showed a significant improvement in their WHO-5 wellbeing scores after 3 and after 6 months of the study.

Other studies have used the WHO-5 Wellbeing Index in adolescents with diabetes, albeit without pharmacist intervention (de Wit et al. 2007, Peyrot et al. 2005 - DAWN Study). Although these studies employed pharmaceutical care in patients with T2DM evaluated only quality of life, they have shown positive results (Sriram et al. 2011, Maxwell et al. 2013).

The baseline wellbeing score of 52.8 in our study was comparable with that of 59.0 in the DAWN study (Peyrot et al. 2005); our patients' score was just above 50, a score indicating low mood. Using this simple instrument, we detected poor wellbeing in 45% of the subjects at baseline, comparable to the 41% reported in the DAWN study (Peyrot et al. 2005), which is not surprising as depression is common among T1DM-affected adolescents (Dantzer et al. 2003, Hood et al. 2006, Lawrence et al. 2006). Our study, however, had no patients with pre-existing depression, as concomitant psychiatric conditions were a study exclusion criterion. During the study, depression was suspected in one female patient according to the Wellbeing Index (WHO-5); this patient was referred to a clinical psychologist.

The improvement in wellbeing seen in our study was both statistically significant and clinically relevant (WHO-5 Wellbeing Index 1998), as demonstrated by a >10% improvement in WHO-5 scores after 6 months. However, since the quality of life in adolescents depends on many factors, in particular on diabetes-specific family conflict, which is tightly linked to lower physical and psychosocial functioning (Laffel et al. 2003), it is difficult to conclusively establish the impact of pharmaceutical care on quality of life and wellbeing (Fressenius Dissertation, 2007). Adolescents in our study had a long diabetes duration (average of 5.9 years) and, as a consequence of physiological changes in puberty, extreme mood swings. Nevertheless, our patients reported that they appreciated periodic monitoring (de Wit at al. 2008) and discussing their wellbeing with the pharmacists, as shown by the improved wellbeing scores, which were not influenced by covariates such as age, sex or diabetes duration, as have been reported elsewhere (Laffel et al. 2003).

In summary, we cannot verify that the improvement in wellbeing scores is solely a result of pharmaceutical care intervention, although a patient-centered approach and empowerment may have contributed to the improvement.

5.3.3. Satisfaction with Pharmaceutical Care (Intervention Group)

Satisfaction with pharmaceutical care questionnaires were given to patients during visits 3 and 6 by the pharmacists. The results of the questionnaires were used primarily as an evaluation of how the adolescent patients perceived the intervention of the

pharmacists, and pharmaceutical care as an additional extension of the healthcare service. To avoid patients providing only positive answers because of the presence of the pharmacists, the patients were left alone to complete the questionnaire. In addition, to confirm the satisfaction ratings, the same questionnaires were given by diabetes educators (nurses) in the clinics to the patients to complete for a second time, without the pharmacists being present. Both sets of results scores were compared (but were not statistically analyzed), and both showed similar satisfaction rates. Pharmaceutical care was assessed as thoroughly positive and quite beneficial by the majority of study participants.

Some patients continued pharmaceutical care visits at their own initiative with their pharmacists, although not to the full extent of the DIADEMA study conditions. After the study, it is up to these pharmacists to assume the responsibility, to decide how and to what extent the subsequent pharmaceutical care visits should take place, and to find new approaches to motivate their adolescent patients to embrace this extended healthcare provider support. By providing pharmaceutical care, pharmacists could help the diabetes team and diabetology practices who usually care for the T1DM youth to overcome the challenges of metabolic control during puberty and to achieve a smoother and easier transition to adulthood.

5.3.4. Drug-Related Problems

The DRPs recorded on a separate form were used by the pharmacists only to identify and name the problems. The identified problems served as “catchwords” and formed the basis for discussion and improvement in the following visits. However, since pharmacists had to perform extensive documentation with the CRFs and develop pharmaceutical care plans, this form (Attachment 12) was used only marginally, and the findings were of minor relevance to the overall study aims.

5.3.5. Adherence to Pediatric Guidelines

Due to time constraints, the total adherence to 12 carefully selected items taken from current pediatric guidelines (ISPAD Guidelines 2009, DDG Guidelines 2010) was recorded by the pharmacists at one random pharmaceutical care visit instead of at visits

one, three and six, as previously planned in the study protocol. Despite this fact, using this simple form (Attachment 13), pharmacists identified non-adherence to selected guidelines.

While recommended screening for prevention of long-term complications was carried out in the majority of patients, some guidelines for the prevention of acute complications (e.g. blood or urinary ketone testing, sick day management, and individualized school plan) were not adhered to, as reported by the patients. Pharmacists advised patients to monitor urine or blood ketones during episodes of uncontrolled hyperglycemia, insulin deficiency, intercurrent illness (sick days), and impending ketoacidosis (Rewers et al. 2009, ISPAD Guidelines 2009). This issue was raised with diabetologists, who consequently prescribed more urinary ketone test strips for the study patients. In addition, individual school plans were created for some patients, for whom adherence problems at school were identified. The school plan, for the management of diabetes at school, should include details such as BG testing, insulin dosing, monitoring of food intake and physical activity, the patient's typical symptoms, and the treatment for hyper-and hypoglycemia (ADA Diabetes Care 2008, DDG Guidelines 2010).

In terms of sick day management, clear guidance should be given to patients and their families for diabetes management during times of inter current illnesses to minimize the risk of complications, such as ketoacidosis, dehydration, uncontrolled or symptomatic hyperglycemia, and hypoglycemia (Brink et al. 2009, ISPAD Guidelines 2009). Study pharmacists detected that this was not done for all patients, and discussed it with the diabetologists. Pharmacists could suggest a written sick day management protocol for the patients, to be provided by the diabetes team.

In summary, a simple instrument with 12 selected guidelines and recorded at only one visit proved to be a useful tool for the prevention of acute complications in our study. Notably, the pharmacist-physician cooperation was extraordinary in both countries, in that suggestions from the pharmacists were received by the physicians with enthusiasm and a positive reception, which may not always be seen in a real-life setting, outside of the DIADEMA study.

5.4. Clinical Relevance of the Study

It is well known that acute and long-term T1DM complications result in considerable premature mortality (Harjutsalo et al. 2011, EDIC 2003). The Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that in adolescents, lowering HbA1c by 1.7% with intensive treatment relative to conventional treatment decreases the risk of retinopathy by 53%, microalbuminuria by 54%, and neuropathy by 60% (EDIC 2003).

Therefore, the HbA1c reduction of 0.54% seen in our DIADEMA study has the potential to be clinically relevant, particularly in high-risk and poorly controlled patients. These patients may benefit from pharmaceutical care, more frequent visits, and extended support of the pharmacists.

Our study pharmacists were selected as they were the study patients' local, regular community pharmacists. A diabetes specialization was not required of the study pharmacists as a prerequisite to participate in the study. As shown in the DIADEMA study, pharmaceutical care in T1DM adolescents can be implemented quickly and successfully, if appropriate tools are available, such as willingness to learn T1DM disease management, apply pharmaceutical care principles and establish good cooperation with diabetologists and diabetes educators.

5.5. Strengths and Limitations of the Study

The strength of our study was its randomized, controlled, and binational study design; the two European study countries had entirely different healthcare systems. An additional strength was the involvement of a multidisciplinary healthcare team, with pharmacists providing extended support and ensuring integrated overall patient care.

Our study has a number of limitations. The short duration implies that the results may become less favorable with a longer study duration, due to decreasing patient motivation (Borus et al. 2010, Frank et al. 2005). Due to time constraints, secondary parameters (e.g. non-severe hypoglycemia, wellbeing, satisfaction with pharmaceutical care) were recorded only for the intervention group.

Another important limitation is the heterogeneous study settings between the two countries—single clinical pharmacist in Bosnia combined with community pharmacists in Germany. Two study sites in two countries are unlikely to represent the general adolescent T1DM population. Furthermore, study patients in our study participated voluntarily, showing self-motivation and appreciation of the efforts from the pharmacists for additional consultation.

Whether the results of this study can be generalized to a wider population of adolescents with T1DM needs to be examined in a larger study group and over a longer period of time. Healthcare differences, including different methods of treatment and counseling, may pose barriers to pharmaceutical care implementation in other settings (van Mill 2001).

5.6. Further Research

In order to achieve a sustainable reduction in HbA1c and improvements in other clinical outcomes, further research that includes homogenous setting (community or clinical) a larger sample size and a longer follow-up is warranted.

5.7. Conclusions

Results of the DIADEMA study suggests that pharmaceutical care may add value and improve T1DM outcomes in adolescents, as shown by a reduction in HbA1c without an increase in hypoglycemia, enhanced wellbeing and high rates of patient satisfaction. Pharmacists were able to provide young people with T1DM with additional and competent support in their diabetes management. Pharmaceutical care and integration of pharmacists into multidisciplinary T1DM teams could potentially help to improve existing care structures and reduce the rate of diabetic complications. Young patients in less developed countries with substantial shortages in healthcare resources, such as Bosnia-Herzegovina, may benefit the most from this integrated approach. Pharmacists should be encouraged to exercise pharmaceutical care, despite any barriers, co-operate with diabetologists and find new approaches for its implementation in routine clinical practice. The DIADEMA study serves as a prime example that this concept is feasible in the practice of pharmacy

6. Final Summary

This thesis presents a comprehensive overview of the DIADEMA study. *Background*: The incidence of T1DM is increasing worldwide. Adherence to therapy regimens decreases during adolescence, resulting in a deterioration of glycemic control, increased morbidity and premature mortality. The benefit of pharmaceutical care (PhC) in adults with T2DM has been widely explored; however, evidence in adolescents with T1DM remains scarce. Therefore, further study was needed to evaluate the effects of PhC in T1DM adolescents. *Objective:* to evaluate the impact of PhC in T1DM adolescents on clinical outcomes (HbA1c levels, incidence of severe and non-severe hypoglycemia, patient satisfaction with PhC, and quality of life). *Setting*: Helios Pediatric Clinic and 12 community pharmacies, in Krefeld, Germany, and the University Pediatric Clinic in Sarajevo, Bosnia-Herzegovina. *Methods:* this was a randomized, controlled, multicenter study including 68 adolescents with T1DM. Patients were randomly assigned to the intervention (n = 40) or control (n = 28) groups. Intervention patients received monthly PhC for 6 months. Control patients received usual care. *Main outcome measures*: the change from baseline in HbA1c and the number of severe hypoglycemia events in the intervention and control groups. Additional outcomes, in the intervention group, were non-severe hypoglycemic events, patient wellbeing, satisfaction with PhC, DRPs and adherence to pediatric guidelines. *Results:* this study showed a significantly greater improvement from baseline in HbA1c in the intervention group versus the control group after 6 months (change from baseline −0.54 vs. +0.32 %, p = 0.0075), with an even more pronounced improvement after only 3 months (−1.09 vs. +0.23%, p = 0.00002). There was no significant between-group difference in the number of severe hypoglycemia events. In the intervention group, there was no significant change from baseline in the frequency of non-severe hypoglycemic events, but a significant improvement in wellbeing and high satisfaction with PhC after 6 months. *Conclusion:* improved clinical outcomes provide new evidence that PhC adds value in the management of T1DM adolescents. However, optimal methods of achieving sustained long-term improvements require further study.

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8. Attachments

Attachment 1: Patient information leaflet

a) Patient information leaflet for parents: Germany

Patienteninformation

(Information für die erziehungsberechtigten Angehörigen)

zur Teilnahme an der Untersuchung

"Beitrag des Apotehekers zur Gesundheit von Jugendlichen in Bosnien-Herzegowina und in Deutschland mit Diabetes Typ 1"

Name des Untersuchungsteilnehmers	***Geburtsdatum des Teilnehmers***
Datum des Gespräches	***Aufklärender Arzt***

Ihr Kind mit Diabetes Typ 1 wird bereits vom erfahrenen diabetischen Team unter Leitung von Frau Dr.med.Müller, Diabetologin und Frau Nemitz, Diabetesberaterin Abteilung für Endokrinologie und Diabetologie, Zentrum für Kinder und Jugendmedizin, Helios Klinik Krefeld betreut.

An dieser Stelle möchten wir Sie über die Möglichkeit zur freiwilligen Teilnahme an einem Projekt "Beitrag des Apothekers zur Gesundheit von Jugendlichen mit Diabetes Typ 1" informieren.

Hintergrund: Ab Herbst 2012 wird ein binationales Projekt zur "Pharmazeutischen Betreuung von Jugendlichen mit Diabetes Typ1 in in Zusammenarbeit mit der Kinderklinik, Abteilung für Endokrinologie und Diabetologie, Helios einen Einfluss auf die I Therapieergebnisse Ihres Kindes hat. Die zusätzliche Betreuung erfolgt durch einen Apotheker odre eine Apothekerin in ihrer öffentlichen Apotheke in Krefeld, der/dielhrem Kind neben der behandelnden Ärztin zur Verfügung steht wird.

Klinik Krefeld, Frau Dr.Müller und Universität Düsseldorf Instut für Klinische Pharmazie und Pharmakotherapie, Prof.dr.med Läer und ausgewählten öffentlichen Apotheken in Krefeld durchgeführt. Das gleiche Projekt wird mit diabetischen Jugendlichen in einem anderen Land,nämlich in Bosnien-Herzegowina, unter gleichen Bedingungen ausgetragen**.**

In der Studie soll untersucht werden, ob die pharmazeutische Betreuung einen Einfluss auf die Therapieergebnisse Ihres Kindes hat. Diese Betreuung erfolgt durch einen Apotheker/in in der öffentlichen Apotheke in Krefeld, der/die Ihrem Kind neben der behandelnden Ärztin zur Verfügung steht.Diabetes mellitus Typ 1 erfordert besonders bei den Jugendlichen und in der Phase der Pubertät eine umfassende Beratung und regelmäßige Betreuung. Viele Jugendliche vernachläßigen Ihre Erkrankung, es kommt infolge der körperlichen Veränderungen und ungleichmäßiger Hormonausschüttung häufig zu Blutzuckerschwankungen, die die Wirkung des Insulins ständig verändern. Eine Blutzuckerkontrolle zu erreichen und die Erkrankung zu kontrollieren, insbesondere in dieser Altersgruppe stellt eine große Herausforderung dar.

Das Ziel dieses Projektes ist es die öffentlichen Apotheken in die Betreuung diabetischer Jugendlichen zu integrieren, um gemeinsam mit dem erfahrenen Diabetesteam der Helios Kinderklinik die Jugendlichen noch engmaschiger zu betreuen. Diese unterstützende, intensivierte pharmazeutische Betreuung soll den Jugendlichen helfen eine bessere Kontrolle der Erkrankung und der Arzneimittelanwendung zu erzielen und basiert vor allem daruf, den jungen Patienten selbst in das Management seiner Diabetes-Erkrankung einzubinden.

Die Betreuung in der Apotheke und außerhalb der gewöhnlichen Klinikbesuche sollen auf Motivation und Vertrauen der Jugendlichen basieren, sowie auf Kommunikation, die die Lösung des Problems anstrebt und Lernen aus Fehlern, aber ohne Schuldzuweisung. Die Jugendlichen können außerhalb der Klinik in einer entspannten Atmosphäre in der Apotheke zusäzlich zum Diabetesteam unterstützt werden, das Diabetesmanagment selbst zu übernehmen und werden in Gesprächen ermutigt ihre Diabetesziele selbst zu definieren und Prioritäten zu setzen. Außerdem können alle Fragen, die Jugendliche häufig zu Insulin und anderen Arzneimitteln haben vom Apotheker direkt beantwortet werden.
Diese Studie dient nicht zur Erprobung von Arzneimitteln.

Durchführung: Jugendliche diabetische Patienten mit Diagnose: Diabetes Typ 1, im Alter von 12 bis 18 Jahren, die seit mindestens 6 Monaten eine schlechte glykämische Kontrolle aufweisen und einen Hb1Ac Wert $\geq$7.5 haben, werden 6 Monate lang intensiv pharmazeutisch betreut. Die pharmazeutische Intervention umfasst mindestens 3 Besuche in der öffentlichen Apotheke. Der Besuch in der Apotheke erfolgt einmal im Monat, bei Bedarf auch mehr. Telefonanrufe vom Apotheker werden ebenfalls angeboten. Nach den ersten drei Monaten wird Ihr Kind wahlweise monatlich entweder telefonisch oder persönlich in der Apotheke für weitere 3 Monate beraten. Die Studiendauer wird insgesamt 6 Monate betragen. Bei den Beratungsgesprächen in den Apotheken wird auf die Einhaltung der diabetischen Leitlinen großen Wert gelegt. Die “multidisziplinäere” Vorgehensweise und Zusammenarbeit mit dem diabetologischen Team der Helios Klinik wird erarbeitet und intensiviert.In der Studie soll untersucht werden, ob die pharmazeutische Betreuung einen Einfluss auf die Therapieergebnisse (Hb1Ac Wert, Anzahl der Hypoglykämien, die festgehalten sind im Tagebuch oder Blutzuckermeßgerät) hat. Ferner wird in der Studie die Lebensqualität des Patienten am Anfang und nach drei und nach sechs Monaten mit einem Fragebogen ausgewertet.Die Zufriedenheit mit der pharmazeutischen Betreuung wird mit einem Fragebogen nach drei Monaten und am Ende der Studie erfasst. Ein Fragebogen zur Selbsteinschätzung des Diabetesmanagements wird ebenfalls ausgefüllt.
Wir werden daher Ihr Kind bitten, zu Beginn, nach drei Monaten und am Ende der Studie diese Fragebögen auszufüllen.
Ferner soll während des Besuches in der Apotheke Blutzucker gemessen und besprochen werden. Ein Tagebuch über die Blutzuckerselbstmessung, Insulineinheiten und Kohlenhydrateinnahme wird vom Patienten täglich ausgefüllt. Insbesondere werden in der Apotheke Blutzuckerwerte der letzten 7 Tage problembezogen ausgewertet. Eine Zusammenfassung des Beratungsgespräch wird an Frau Dr. Müller weitergeleitet.
Der Apotheker steht Ihnen und Ihrem Kind neben der behandelnden Ärztin zur Verfügung, arzneimittelbezogene Probleme und eine individuelle auf Ihr Kind bezogene Diabetes Beratung anzubieten.
Diese Studie hat einen unterstützenden, beratenden Charakter und dient nicht zur Erprobung von Arzneimitteln.

Mögliche Risiken: In dieser Studie bestehen keinerlei Risiken für den Patienten, da die ärztliche Therapie und Entscheidung in keinerlei Weise beeinflusst wird. Die Apotheker in dieser Studie bieten lediglich eine unterstützende Beratung und Betreuung an, die das diabetische Team aus der Helios Kinderklinik unterstützen soll, eine bessere Kontrolle der Erkrankung zu erreichen.

a) Patient information leaflet for parents: Germany (continued)

Die Ergebnisse der Studie sollen dabei helfen den Einfluss einer zusätzlichen pharmazeutischen Betreuung zu bewerten, sowie dazu beitragen, die zukünftige Versorgung von Kindern und Jugendlichen mit Diabetes Typ 1 noch weiter durch eine interprofessionelle Zusammenarbeit zwischen Arzt und Apotheker zu verbessern.

Verwendung der klinischen Daten: Alle drei Monate, d.h. zweimal im Verlauf der Studie wird der glykolysierte Hämoglobin: HbA1c bestimmt und zwar im Rahmen des üblichen Klinikbesuches. Dieser Wert sowie Anzahl der Hypoglykämien sollen nach 6 Monaten ausgewertet werden, um den Effekt der intensiven pharmazeutischen Betreuung auf die Blutzuckerkontrolle zu beurteilen.

Was bedeutet die Teilnahme für Sie? Ihre Teilnahme an dieser Studie ist freiwillig. Ihr Kind ist jederzeit berechtigt, auch ohne Angabe von Gründen, aus der Studie auszuscheiden, ohne dass Ihrem Kind dadurch Nachteile für seine weitere ärztliche Behandlung entstehen.

Alle im Rahmen der Untersuchung erhobenen und gewonnenen klinischen und persönlichen Daten werden ausschließlich anonymisiert in der Apotheke gespeichert und ausgewertet, ohne Nennung des Namens und der Adresse. Alle persönlichen Angaben, die Sie bzw.Ihr Kind uns mitteilen, Information zum Gesundheitszustand Ihres Kindes, sowie die Inhalte der Beratungsgespräche und klinische Ergebnisse werden vertraulich behandelt. Arzt und Apotheker unterliegen der Schweigepflicht. Weiterhin werden die Bestimmungen des Bundesdatenschutzgesetzes eingehalten. Die personengebundenen Daten werden von uns vertraulich behandelt und nicht an unbefugte Dritte weitergegeben bzw. übermittelt.

a) Patient information leaflet for adolescent patients: Germany

Patienteninformation

(Information für einsichtsfähige Kinder und Jugendliche)

zur Teilnahme an der Studie

"Beitrag des Apothekers zur Gesundheit von Jugendlichen mit Diabetes Typ 1"

Name des Untersuchungsteilnehmers ***Geburtsdatum des Teilnehmers***

Datum des Gespräches ***Aufklärender Arzt***

Zur Behandlung Deines Diabetes Typ 1 wirst Du in regelmäßigen Abständen von Deinem erfahrenen diabetischen Team Frau Dr.Müller und Frau Nemitz in der Helios Klinik in Krefeld betreut. Wir möchten Dich heute über die Möglichkeit zur **freiwilligen** Teilnahme an einer Studie informieren.

Viele Jugendliche haben aufgrund der körperlichen Veränderungen in der Wachstumsphase Schwierigkeiten eine Blutzuckerkontrolle zu erreichen.

Es kommt infolge dieser Veränderungen und ungleichmäßiger Hormonausschüttung häufig zu Blutzuckerschwankungen, die die Wirkung des Insulins ständig verändern. Eine Blutzuckerkontrolle zu erreichen und die Erkrankung zu kontrollieren stellt eine große Herausforderung dar.

Diabetes mellitus Typ 1 erfordert besonders bei den Jugendlichen und in der Phase der Pubertät eine umfassende Beratung und regelmäßige Betreuung.

Um eine bessere Kontrolle der Blutzuckerwerte zu erreichen, bieten wir Dir, dass Du neben Deiner Ärztin und Deiner Diabetesberaterin aus der Klinik, zusätzlich, wenn Du Insulin in Deiner Apotheke holst, einmal im Monat von einem Apotheker beraten wirst.

Wir glauben, daß eine zusätzliche Person, nämlich Dein Apotheker oder Apothekerin, Dich zu allen Fragen und Problemen die Du hast, im Zusammenhang mit Diabetes, unterstützen kann.Wenn Du an der Studie teilnimmst, solltest Du mindestens einmal im Monat Deine Apotheke besuchen und in einem Gespräch mit dem Apotheker/in gemeinsam Dein Tagebuch mit allen Werten anschauen und auswerten. Dabei soll eine gemeinsame Lösung, auf Deinen Alltag angepasst gefunden werden.Dein/e Apotheker/in kann Dich auch jederzeit anrufen oder Du ihn, falls noch Fragen offen sind

Dein/e Apotheker/in wird Dir Fragebögen geben am Anfang, nach drei Monaten und am Ende der Studie, die Du alleine ausfüllen solltest.Wenn Du an dieser Studie teilnimmst, bist Du an einem internationalen Projekt beteiligt, das helfen soll auch andere Kinder und Jugendliche mit Diabetes Mellitus in Deutschland und in anderen Ländern noch besser zu betreuen.

Es ist uns sehr wichtig, dass Du verstehst, dass Du uns **jederzeit** sagen kannst, ob Du mit dieser Studie einverstanden bist oder nicht. Du kannst uns auch jederzeit alle Fragen zur Untersuchung stellen; wir erklären Dir gern alles, was Du wissen möchtest.

b) Patient information leaflet for parents and adolescent patients: Bosnia-Herzegovina

INFORMACIJA ZA PACIJENTA

DIADEMA STUDIJA
„Famaceutska njega adolescenata sa Diabetes Mellitusom Tip"

_____	_____
Ime i prezime pacijenta	Datum rođenja
_____	_____
Ime i prezime ljekara	Datum razgovora

Vi već dolazite na pedijatrijsku kliniku Sarajevo i pod nadzorom ste vašeg iskusnog dijabetološkog tima dr.Sniježane Hasanbegović i sestre Sene Kalajdzisalihović zbog liječenja Dijabetes tipa 1.

Željeli bismo vas obavijestiti o tome da dobrovoljno možete sudjelovati u DIADEMA studiji.

Zbog fizioloških promjena u fazi rasta i adolescencije dolazi do poteškoća u postizanju kontrole glikemije. Često i kao rezultat tih promjena i neujednačenog lučenja hormona dolazi do fluktuacije šećera u krvi, koje direktno utiču i na dejstvo insulina. Diabetes mellitus tip 1, posebno kod mladih i u fazi puberteta, iziskuje sveobuhvatne savjete i redovno podršku. U doba puberteta veliki je izazov postići kontrolu glikemije i kontrolu dijabetesa, što zahtijeva veću njegu i kontinuiranu edukaciju i nadzor.
Da bi se postigla bolja kontrola šećera u krvi nudimo vam dodatnu uslugu „ Farmaceutsku njegu" od strane dr.pharm Emine Obarcanin. Uz naš dijabetološki tim dr. Obarcanin može vas dodatno podržati i odgovoriti na pitanja i probleme koje su povezani sa dijabetesom.

Ako želite učestvovali u studiji , trebali biste posjetiti kliniku i dr.Obarcanin barem jednom mjesečno u trajanju od 6 mjeseci i ponijeti svoj dnevnik sa šećerima. Ukoliko postoje problemi sa šećerima i prilagodjavanjem doze inzulina, dr.Obarcanin će s vama nastojati pronaći zajedničko rješenje koje je prilagođeno vašem svakodnevnom životu. Vaš klinički farmaceut, t.j. dr. Obarcanin može vam pružiti savjet i ako je nazovete telefonom ili ako imate bilo kakvih dodatnih pitanja.

Na početku , nakon tri mjeseca i na kraju studije, nakon 6 mjeseci klinički farmaceut, dr. Obarcanin će vam dati upitnike da odgovorite.
Ukoliko učestvujete u ovoj studiji, bićete uključeni u binacionalni projekat, sa ciljem da se još više pomogne djeci sa Diabetes mellitusom. Isti ovakakav projekat ima istovremeno i u Njemačkoj i nadamo se uskoro u drugim zemljama.

Veoma je važno da da nam možete reći u bilo koje vrijeme , ako niste saglasni sa ovom studijom. Možete prekinuti vaše sudjelovanje u bilo kojem trenutku , bez razloga i oblašnjenja zašto više ne želite da učestvujete. Ako više ne želite sudjelovati, to neće imati nikakvog utjecaja na vašu dalju zdravstvenu skrb kod nas. Uvijek možete pitati sva pitanja vezano za studiju, a da Vam mi objasnimo sve što vas zanima.

Attachment 2: Informed consent form

a) Informed consent form for parents: Germany

Einverständniserklärung

für die Erziehungsberechtigten Angehörigen zur Teilnahme an der Untersuchung "Beitrag des Apothekers zur Gesundheit von Jugendlichen mit Diabetes Typ 1"

Name des Patienten in Druckbuchstaben:

.....
Name des Erziehungsberechtigten:

.....

Geb. Datum (Patient): .....

Code: .....

Ich erkläre mich bereit, daß mein Kind an der Untersuchung "Beitrag des Apothekers zur Gesundheit von Jugendlichen mit Diabetes Mellitus Typ 1" teilnimmt.

Ich bin von Frau Dr.med. Müller ausführlich und verständlich über das Projekt, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der Untersuchung, und die sich für mein Kind daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 8 Seiten umfaßt, gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügendbeantwortet. Ich hatte ausreichend Zeit, mich für die Teilnahme meines Kindes zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.Ich werde zusammen mit meinem Kind den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, die freiwillige Mitwirkung meines Kindes jederzeit zu beenden, ohne daß daraus meinem Kind Nachteile für weitere medizinische Betreuung entstehen.Ich bin zugleich damit einverstanden, daß im Rahmen dieser klinischen Studie ermittelten Daten von meinem Kind aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte des Studienleiters und der zuständigen Behörden beim Prüfarzt Einblick in personenbezogenen Krankheitsdaten meines Kindes nehmen.Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt. Die Information in der oben beschriebenen Einverständniserklärung wurde meinem Kind beschrieben und mein Kind ist mit der Teilnahme an der Untersuchung einverstanden.

.....
(Datum und Unterschrift des Erziehungsberechtigten)

.....
(Datum, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient/Erziehungsberechtigter erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Prüfarztes.)

b) Informed consent form for adolescent patients: Germany

<u>Einverständniserklärung</u>

für den Patienten zur Teilnahme an der Untersuchung

"Beitrag des Apothekers zur Gesundheit von Jugendlichen mit Diabetes Typ 1"

Name des Patienten in Druckbuchstaben:

……..

Geb.Datum: ……..

Code:……

Ich erkläre mich bereit, an der Untersuchung Beitrag des Apothekers zur Gesundheit der Jugenlichen mit Diabetes Mellitus Typ 1 teilzunehmen.

Ich bin von Frau Dr.med.Müller ausführlich und verständlich über die Untersuchung, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der Untersuchung, und die sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 8 Seiten umfaßt, gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne daß mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, daß meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte des Studienleiters und der zuständigen Behörden beim Prüfarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

……
(Datum und Unterschrift des Patienten)

……
(Datum, Name und Unterschrift des verantwortlichen Arztes)

c) Informed consent form parents and adolescent patients: Bosnia-Herzegovina

Informirani pristanak
DIADEMA Studija

"Farmaceutska njega adolescenata sa Diabetes Mellitusom Tip"

Ime pacijenta (štampanim slovima) : .....

Ime roditelja ili staratelja : .....

Datum rođenja (pacijenta) : ..... Code : .....

Ja pristajem da ja /da moje dijete učestvuje u studiji " Farmaceutska njega adolescenata sa Diabetes Mellitusom Tip 1"

Informisan sam detaljno o studiji od dr.Hasanbegović . Saglasan sam da ispoštujem studijske procedure i da dolazim, t.j. moje dijete na savjetovanje kod farmaceuta barem jednom mjesečno u toku 6 mjeseci.

Zadržavam pravo da prekinem dobrovoljno učešće moje ili mog djeteta u bilo koje vrijeme ako to odlučimo.

Također se slažem da se klinički podaci moji/ mog djeteta u ovom ovom kliničkom ispitivanju anonimno pohrane i analiziraju

.....(Potpis roditelja ili staratelja)

.....(Potpis pacijenta)

.....(Potpis ljekara)

.....Datum

Zaštita podataka i privatnost: Svi prikupljeni podaci, tokom studije i lične podaci anonimno će se pohraniti i analizirati, bez spominjanja imena vašeg djeteta ili adrese. Svi osobni podaci i podaci koje ste nam dali o svom zdravlju, kao i sadržaj savjetovanja i kliničkih ishoda će se čuvati u tajnosti. Liječnik i farmaceut podliježu zakonu o profesionalnoj povjerljivosti i zaštiti ličnih podataka. Takodje odredbe i zakoni o zaštiti podataka će se ispoštovati . Vaši osobni podaci će se tretirati kao povjerljivi i neće se otkriti niti prenositi neovlaštenim trećim licima. Svi podaci će se koristiti anonimno. Ako se ne slažete sa studijom, možete opozvati u pisanom obliku daljnje korištenje vaših podataka. Vaši unosi podataka će biti izbrisani odmah.Nakon regularnog završetka studije ili nakon prekida studije vaši podaci će se čuvati deset godina. Nakon toga, lični podaci će biti izbrisani ako neka druga pravna, zakonska odredba ne zahtjeva drugačije.

Attachment 3: DIADEMA study Standard Operating Procedure and data flow according to GCP-ICH Guidelines

DIADEMA: Standard Operating Procedure (SOP) gemäß GCP-ICH Guidelines

Gegenstand/Ziele : Dataflow (Datenaustausch) und Studiendokumentation Autor: E.Obarcanin Datum:_____Unterschrift: Freigabe: Prof.Dr.med.Läer Datum:_____ Unterschrift:	SOP No.: DIA-001 Version No.: 1.0 Datum: 27.12.2012 Seite 1 von 9

Dataflow (Datenaustausch) und Studiendokumentation

Inhalt

DIADEMA Standard Operating Procedure (continued)

1. Gegenstand/Ziele der SOP

Die während der DIADEMA Studie erhobenen klinischen Daten, die im Protokoll definiert sind, sollen von der Helios-Klinik Frau Müller und/oder Diabetesberaterin Frau Nemitz an die beteiligten Apotheken **gefaxt** werden. Diese Daten dienen der Beurteilung des Einflußes einer pharmazeutischen Betreuung bei Jugendlichen mit Diabetes Typ1 einschließlich der Genauigkeit, Vollständigkeit, Plausibilität, Lesbarkeit und Aktualität der Studiendokumentation und tragen grundlegend zur Qualität der Daten und derer statistischen Auswertbarkeit bei.

Dokumentationsbögen bzw. CRF (case report form) gelten zudem als Beweismittel für die protokollgerechte Durchführung der Studie

Diese SOP regelt grundsätzlich die **Art und Weise** wie die die **Eintragungen in den Dokumentationsbögen getätigt werden und wie die klinische Daten von der Helios Klinik auf die Apotheken übertragen werden .** Ferner regelt diese SOP wie die Berichte und pharmazeutische Pläne an die Ärztin in der HELIOS Klinik vermittelt werden.

Die Gute Klinische Praxis (GCP, Good Clinical Practice) ist ein internationaler ethischer und wissenschaftlicher Standard für Planung, Durchführung, Dokumentation und Berichterstattung von klinischen Prüfungen am Menschen. Die Einhaltung dieses Standards schafft öffentliches Vertrauen, daß die Rechte, die Sicherheit und das Wohl der Prüfungsteilnehmer gemäß der Deklaration von Helsinki geschützt werden und die bei der klinischen Prüfung erhobenen Daten glaubwürdig sind.

Wesentliche Voraussetzung für die Erlangung valider Studiendaten ist die korrekte Sammlung und Erfassung von Patientendaten sowohl in den Originaldokumenten als auch in den CRF (Case Report Form) und die korrekte Weiterleitung. Dieser Bedeutung trägt ICH-GCP Rechnung, indem hier präzise Vorgaben zum Ausfüllen und Umgang von CRFs gemacht werden mit dem Ziel, dass Studiendaten

- genau
- vollständig lesbar und zeitgemäß dokumentiert und weitergegeben werden
- die Dokumentation nachvollziehbar ist und auch bei Korrekturen nachvollziehbar bleibt (ICH-GCP, Kapitel 4.9; besonders 4.9.3).

3. Grundsätzliches

Die Daten, die erhoben werden, sollen in Übereinstimmung mit den Originalunterlagen (Quelldaten, Source data) in die Arztdokumentationsbögen durch Prüfärztin Frau Müller oder durch Diabetesberaterin Frau Nemitz übertragen werden. Hierbei sind die Vorgaben im Protokoll der DIADEMA Studie zu beachten. Dokumentationsbögen werden vom Projektleiter E.Obarcanin der DIADEMA Studie zur Verfügung gestellt. Es gibt einen Dokumentationbogen für den Arzt: Arztdokumentationsbogen (CRF Seiten 1-3) und einen Dokumentationsbogen für Apotheker: Apothekerdokumentationsbogen (CRF Seiten 1-10)

Eintragungen im CRF dürfen nur die zur Dokumentation berechtigten Personen vornehmen. Diese müssen im Studienordner in einer Liste mit Unterschriftenprobe / Kürzel erfasst sein Jeder vervollständigte Prüfbogen muss mit Datum und Unterschrift (bzw. Kürzel) versehen werden.

Der CRF ist sinngemäß Bestandteil der Krankenakte eines Patienten und ist Teil der Dokumentation des Patienten. Der CRF muss deshalb bei Weitergabe an den Projektleiter als Kopie im Prüfzentrum gelagert werden.Alle Daten, die im CRF dokumentiert werden, müssen auch in der Patientenakte zu finden sein.

4. Datenfluß (Dataflow)

Arzt

Die Daten, in Übereinstimmung mit den Originalunterlagen (Quelldaten, Source data) werden von Prüfärztin Frau Müller oder Diabetesberaterin Frau Nemitz in den **Arztdokumentationsbogen** (Arzt CRF) übertragen. Der Arztdokumentationsbogen, der 3 Seiten beinhaltet, wird unterschrieben und an die betreuende Apotheke **gefaxt**. Das Orginal (unterschrieben von Prüfärztin Frau Müller und/oder Diabetesberaterin Frau Nemitz sofern sie die CRFs ausgefüllt hat) wird in den Ärzteprüfordner (Investigator Site File, ISF) abgelegt.

Die Daten von der Helios Kinder Klinik werden insgesamt **dreimal** an die jeweiligen Apotheken gefaxt

- vor der Studie (voraussichtlich im Januar 2013)
- nach drei Monaten
- nach 6 Monaten.

Nach dem Studienprotokoll sollen alle Apotheken den pharmazeutischen Plan/Bericht nach 3 und nach 6 Monaten der Studie an die Prüfärztin faxen (emailen/scannen). Dieser Fax/Email wird ebenfalls im Ärzteprüfordner abgelegt.

Die Originalarztdokumentationsbögen (Arzt CRFs) werden im Arztprüfordner gelagert. Nach 3 Monaten und nach 6 Monaten werden diese an die Projektleiterin E.Obarcanin persönlich abgegeben.

Eine Kopie von allen Arztdokumentationsbögen (Arzt CRFs) verbleibt im Prüfzentrum Helios Klinik.

Apotheker

Der betreuende Apotheker bekommt den **dreiseitigen Arztdokumentationsbogen (Arzt CRF)** gefaxt von der Helios Klinik und legt diesen in den **Apothekerprüfordner** ab.

Der Apotheker füllt den Apothekerdokumentationsbogen (Apotheker CRF), der für den jeweiligen Besuch des Patienten vorgefertigt ist aus, unterschreibt jede Seite und legt es in den Apotheker prüfordner ab. Für verschiedene Termine sind unterschiedliche Bögen auszufüllen

Beim Besuch des Patienten Nummer 1, 3 und 6 wird zu dem Apothekerdokumentationsbogen auch der per Fax erhaltene Arztdokumentationsbogen (Arzt RF) in den Apothekerprüfordner abgelegt.

Nach den Besuchen 3 und 6 (nach Monat 3 und 6 Monaten der Studie) wird der Plan/Bericht des Apothekers (Apotheker CRF Seite 4) an die Prüfärztin/Diabetesberaterin gefaxt. **(Fax Nr: 02151 321926)**

Am Anfang der Studie (Besuch1) , nach drei Monaten (Besuch 3) und am Ende der Studie (Besuch 6) werden die Lebensqualität sowie die Einhaltung der pädiatrischen Richlinien im Apotheker CRF festgehalten. Nach Besuch 3 und 6 wird zusätzlich der Fragebogen “Zufriedenheit mit der pharmazeutischen Betreuung“ ausgefüllt. Die Apotheker CRFs werden um diese Fragebögen erweitert und wird bereitgestellt durch den Projektleiter (Monitor) E.Obarcanin.

Die Original-Apothekerdokumentationsbögen (Apotheker CRFs) werden im Apothekerprüfordner gelagert. Nach 3 Monaten und nach 6 Monaten werden diese an Projektleiterin Frau Obarcanin persönlich ab gegeben. Eine Kopie von allen Apothekerdokumentationsbögen (Apotheker CRFs) verbleibt in den jeweiligen Apotheken (Prüfzentren).

Projektleiter (Monitor E.Obarcanin)

Der Projektleiter (Monitor) sammelt alle CRFs nach drei und nach 6 Monaten der Studie persönlich ein.

5. Verantwortlichkeiten

Gemäß ICH-GCP 4.9.1 sollte der Prüfer (Prüfarzt, Prüfapotheker) die Genauigkeit, Vollständigkeit, Lesbarkeit und Aktualität der Daten gewährleisten, die in den CRF und in allen geforderten Berichten an den Studienleiter weitergeleitet werden. Er bestätigt dies mit seiner Unterschrift unter dem CRF. Um auch die Aktualität der Daten zu bestätigen, muss die Unterzeichnung mindestens für jeden Besuch erfolgen.

Arzt

Der Prüfarzt der Untersuchung ist dafür verantwortlich, von jedem an der Untersuchung teilnehmenden Patienten nach Aufklärung über Ziele, Methoden, Nutzen und mögliche Risiken der Prüfung eine Einwilligungserklärung einzuholen. Die Einwilligung muss vorliegen, bevor der Patient irgendwelchen Maßnahmen im Rahmen der Studie (z.B. Beratung in der Apotheke) unterzogen wird. Jedem Patienten bzw. dessen gesetzlichem Vormund muss klar und unmissverständlich mitgeteilt werden, dass es ihm freisteht, die Teilnahme an der Studie abzulehnen, oder dass er seine Einwilligung jederzeit und aus beliebigen Gründen zurückziehen kann, ohne dass ihm daraus ein Nachteil entsteht.

Weiterhin liegt die Verantwortung für die korrekte Übertragung der Quelldata (Source data)und Weiterleitung der Daten an die Prüfapotheker im Prüfzentrum beim Prüfarzt (ICH-GCP 4.9.1.)

Prüfazt soll die Adverse Events sowie SAE dokumentiern und an den Studienleiter weiterleiten.

Ausgefüllte Dokumentationsbögen müssen als Teil des Arztprüfordners (ISF) sicher für berechtigte Personen zugänglich aufbewahrt werden

Apotheker

Die Verantwortung für die korrekte Dokumentation der pharmazeutischen Betreuung, nach dem Studienprotokoll und für Festhalten der Daten in dem Apothekerprüfbogen (Apotheker CRF) trägt der Apotheker.

Prüfapotheker hat die Verantwortung die Adverse Events zu dokumentieren und sowie **schwere AE ggf.SAE** zu dokumentiern und an den Prüfarzt **weiterzuleiten.**

Ein korrektes und vollständiges Ausfüllen der CRF trägt dazu bei, Rückfragen ("Querys") und gegebenenfalls nachträgliche Änderungen der erfassten Daten zu reduzieren. Ausgefüllte Dokumentationsbögen müssen als Teil des Apothekerprüfordners (ISF) sicher für berechtigte Personen zugänglich aufbewahrt werden

Projektleiter (Monitor)

Hat die Verantwortung für die gesamte Überprüfungung der Studiendokumentation der Patientendaten (Monitoring) sowie für Aufklärung der Unstimmikeiten (Queries). Der Monitor ist verantwortlich dafür die Originale der CRF-Seiten nach drei und nach sechs Monaten der Studie einzusammeln. Außerdem ist der Monitor der Untersuchung dafür verantwortlich, ordnungsgemäße Aufzeichnungen über die Untersuchung zu führen.

Studienleiter

Hat die Verantwortung die gesamten Studenunterlagen ordnungsgemäß am Institut für Klinische Pharmazie und Pharmakotherapie an der Heinrich-Heine-Universität Düsseldorf zu archivieren, sowie vertrauliche Behandlung der Unterlagen zu gewährleisten.

6. Allgemeine Dokumentationsregeln

- Die Dokumentationsbögen müssen gut lesbar mit schwarzem Kugelschreiber ausgefüllt werden.
- Eventuelle Fehler dürfen nicht unkenntlich gemacht werden, sondern sind mit einer einzigen Linie durchzustreichen. Danach ist die Korrektur einzutragen, vom Leiter der Untersuchung oder vom zuständigen Studienassistenten mit Datum und Initialen zu versehen und abzuzeichnen.

- Alle Felder eines Prüfbogens müssen ausgefüllt werden (wenn das Protokoll nichts anderes vorsieht). Es muss jedes Feld als bearbeitet erkennbar sein, damit ersichtlich ist, ob etwas vergessen wurde, nicht durchgeführt wurde oder nicht zutrifft.
- Falls keine Antwort zutrifft, werden die betreffenden Felder durchgestrichen und daneben vermerkt: n.a. = not applicable (nicht zutreffend).
- Wenn etwas nicht durchgeführt wurde, werden die betreffenden Felder durchgestrichen und daneben vermerkt: n.d. = not done (nicht durchgeführt).
- Falls die Antwort auf die betreffenden Fragen nicht bekannt ist, werden die betreffenden Felder ebenfalls durchgestrichen und daneben vermerkt (– je nachdem, was in evtl. vorhandenen Dokumentationsrichtlinien vorgegeben ist): Diese sollten jedoch sparsam und möglichst nicht ohne Begründung verwendet werden.
- Auf jeder Seite des CRF werden die Identifizierungsmerkmale des jeweiligen Patienten (Patientennummer,Besuchsnummer und Datum) abgefragt. Diese Kopfzeile muß unbedingt ausgefüllt werden, um eine eindeutige Zuordnung zu gewährleisten.
- Bemerkungen und Kommentare sollten möglichst gut lesbar in die hierfür vorgesehenen Freitext-Felder geschrieben werden.
- Laborbefunde, Arztbriefe, etc., welche der Dokumentation beigefügt werden sollen, müssen anonymisiert und mit der Patientennummer versehen werden. Um Vertraulichkeit zu gewährleisten, darf der Name der Versuchsperson **niemals** im Prüfbogen oder irgendeinem anderen Dokument erscheinen, das dem Projektleiter zurückgegeben wird.

7. Dokumentation von AEs und SAEs

Unerwünschte Ereignisse (AE=adverse events) sollen in Übereinstimmung mit dem Protokoll in der Patientenakte, im CRF (auf dem betreffenden Erhebungsbogen) und falls schwerwiegend, zusätzlich auf dem entsprechenden SAE-Bogen (Serious adverse event) dokumentiert werden. SAE-Bögen müssen immer vom **Prüfarzt** unterschrieben werden.
Im Falle eines schwerwiegenden unerwünschten Ereignisses muss innerhalb von 24 Stunden per Telefon oder Telefax Verbindung mit dem Leiter der Untersuchung aufgenommen werden:

Frau Prof. Dr. med. Stephanie Läer
Institut für Klinische Pharmazie und Pharmakotherapie
Heinrich-Heine-Universität Düsseldorf
Universitätsstr. 1, Geb. 26.22.02.2140225 Düsseldorf
☎ +49 211 - 81-10740 +49 211 - 81-10741
stephanie.laeer@uni-duesseldorf.de

8. Meldung an die Ethikkommission

Während des Untersuchungszeitraumes wird jeder bekannt gewordene Verdachtsfall eines SAE der zuständigen Ethikkommission angezeigt.

9. Studienende, Studienabbruch, Widerruf der Teilnahme

Gegebenenfalls sind für das Studienende Abschlussuntersuchungen und für die Nachbeobachtungsphase Follow-Ups zu dokumentieren.Auch der Studienabbruch (withdrawal, Therapiestop) von in die Studie aufgenommenen Patienten soll erfasst werden, wenn möglich unter Angabe von Gründen.Wenn der Patient seine Enwilligung zur Studienteilnahme widerruft sollen die Daten in anonymisierter Form weiterhin für die Studie verwendet werden dürfen. Es wird dem Erziehungsberechtigten bzw. dem Kind jedoch eingeräumt, die Verarbeitung der personenbezogenen Daten schriftlich jederzeit widerrufen zu können, wenn dies nach dem Widerruf der Einwilligung nicht mehr erwünscht ist.

10. Korrekturen

Laut Kapitel 4.9.3, ICH-GCP Leitlinie, sollten alle Änderungen oder Korrekturen an einem Prüfbogen mit Datum, Initialen und (falls erforderlich) mit einer Erklärung versehen sein und das Original nicht verdecken. Eintragungen im CRF müssen demnach folgendermaßen berichtigt werden:

- keine Korrekturflüssigkeiten wie z.B. Tipp-Ex verwenden, nicht radieren
- falsche Einträge mit einem einzigen Querstrich durchstreichen, so dass sie lesbar bleiben
- die richtigen Angaben daneben schreiben, ggf. mit Begründung
- die Änderungen mit Datum und Namenskürzel abzeichnen

Damit die geforderte Nachvollziehbarkeit gewährleistet ist, sollten Aufzeichnungen über Änderungen und Korrekturen aufbewahrt werden.Auf die im Prüfzentrum verbleibenden Durchschläge / Kopien dürfen keine weiteren Eintragungen gemacht werden, sobald die Originale zur Datenerfassung gegeben bzw. vom Projektleiter (Monitor)eingesammelt wurden. Für nachträglich notwendige Korrekturen sollte gegebenenfalls ein Data Correction Form (Dokumentationsblatt als Ergänzung zum CRF) verwendet werden.

11. Nachträgliche Änderungen von Daten im CRF (Queries)

Nachträgliche Änderungen von Daten im CRF z.B. auf Grund von Rückfragen (Queries) werden auf den CRF-Kopien eingetragen und diese werden an den Monitor weitergeleitet. Zur Beantwortung der Queries werden Eintragungen auf dem ursprünglichen CRF durch den Prüfer korrigiert oder ergänzt und Informationen weitergegeben.Die Genauigkeit, Vollständigkeit, Lesbarkeit und Aktualität der Daten ist vom Prüfer mit seiner datierten Unterschrift zu bestätigen. Das Original der Queries wird vom Monitor eingesammelt. Eine Kopie verbleibt im Prüfzentrum und wird zusammen mit der CRF-Kopie abgelegt.

12. Vorlagen

DIADEMA-SOP DIA 001: Dataflow und Studiendokumentation, Version 1,
vom 27.12.2012

13. Änderungen Keine, da Ersterstellug

Attachment 4: Adverse events form

Adverse event form

STUDY NAME: DIADEMA	
Site: Bosnia or Germany **Patient Number :**	

Has the participant had any Adverse Events during this study? ☐ **Yes** ☐ **No** ***(If yes, please list all Adverse Events below)***

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = Resolved, No Sequel 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-not treated 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (If yes, complete SAE form)

Adverse Event	Start Date	Stop Date	Severity	Relationship to Study Treatment	Action Taken	Outcome of AE	Expected?	Serious AE?	Initials
1.									
2.									
3.									

Attachment 5: Serious adverse events form

Serious Adverse Event (SAE) Report Form

Protocol Title: DIADEMA STUDY	
Protocol Number: 3991_____ **Site Number:** _____ **Patient Number :** _____	

1. SAE Onset Date: _____ (dd/mm/yyyy)
2. SAE Stop Date: _____(dd/mm/yyyy)
3. Location of serious adverse event: _____
4. Was this an unexpected adverse event? Yes ☐ No ☐
5. Brief description of participant(s) with no personal identifiers:
   Sex: F ☐ M ☐ Age: _____
6. Brief description of the nature of the serious adverse event (attach description if more space needed):
   _____
   _____
7. Category of the serious adverse event:

☐ death – date __/___/___(dd/mmm/yyyy) ☐ congenital anomaly / birth defect

☐ life-threatening ☐ required intervention to prevent

☐ hospitalization-initial or prolonged permanent impairment

☐ disability / incapacity ☐ other:_____

8. Intervention type:

☐ Medication or Nutritional Supplement: specify_____

☐ Device: Specify: _____

☐ Surgery: Specify: _____

☐ Behavioral/Life Style: Specify: _____

9. Relationship of event to intervention:

Serious Adverse Event (SAE) Report Form (continued)

☐ Unrelated (clearly not related to the intervention)

☐ Possible (may be related to intervention)

☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event? ☐ Yes ☐ No

11. What medications or other steps were taken to treat serious adverse event?

_____

_____

12. List any relevant tests, laboratory data, history, including preexisting medical conditions

_____

_____

13. Type of report:

☐ Initial

☐ Follow-up

☐ Final

Signature of Principal Investigator: _____ Date: _____

In the event of SAE (within 24 hours), please contact immediately:

In Bosnia:
DIADEMA Study Cooridnator : Emina Obarcanin
☎ +387 62 649 298
Email: emina.obarcanin@hotmail.com

In Germany:
DIADEMA Study leader: Prof. Dr. med. Stephanie Läer
☎ +49 211 - 81-10740 +49 211 - 81-10741
stephanie.laeer@uni-duesseldorf.de

Attachment 6: DIADEMA study data flow (brief manual)

HINWEISE ZUM DATAFLOW (Datenaustausch)

ARZT: Zu Beginn (Baseline), Besuch 3 und 6

- Arzt oder Diabetesberaterin füllt ARZT- CRF vollständig aus
- Unterschreibt jede Seite des CRFs
- Faxt klinische Daten an die Apotheken
- Dokumentieren AE bzw. informieren den Studienleiter im Fall eines SAE
- Legen die Orginal-CRFs in den Arztprüfordner ab
- Nach 3 Monaten und nach 6 Monaten werden CRFs an Projektleiter persönlich abgegeben
- Eine Kopie von allen Arzt CRFs verbleibt in der Helios Klinik

APOTHEKER: Besuch 1,2,3,4,5 und 6

- Legt das Fax (Arzt CRF) zu dem jeweiligen Besuch in den Prüfordner ab
- Apotheker füllt Apotheker -CRF für jeden Besuch des Patienten vollständig aus
- Dokumentieren AE bzw. faxen schwere AE oder SAE an den Arzt
- Unterschreibt jede Seite des CRFs
- Apotheker lagert Orginal-CRFs in den Apothekerprüfordner ab
- Nach 3 Monaten und nach 6 Monaten werden CRFs an Projektleiter persönlich abgegeben
- Eine Kopie von allen Apotheker CRFs verbleibt in der Apotheke

Besuch 3 und Besuch 6 (Apotheker)

- Apotheker faxt /emailt Plan/Bericht (Seite 4 CRF) an die Helios Klinik
- Füllt FB Lebensqualität (Besuch 1,3,6) und FB Zufriedenheit (Besuch 3,6) aus

Fax Nummer Helios Klinik 02151/321926 (Frau Nemitz)

Email: verena.nemitz@helios-kliniken.de

Telefon: 02151 324495

Bei allen Fragen : emina.obarcanin@uni-duesseldorf.de; **+ 387 62649298**

oder Herr M.Krüger: m.krueger@linner-apotheke.de; **+ 02151 570355**

DIADEMA study data flow (brief manual) (continued)

HINWEISE ZUR DOKUMENTATION

Einträge im CRF (Dokumentationsbögen) :

- Handschriftliche Einträge oder Korrekturen bitte mit schwarzem Dokumenten echten Stift (Kuli) vornehmen.
- Bitte achten Sie auf Lesbarkeit und Vollständigkeit.(Wir haben uns bemüht, die CRFs weitgehend selbsterklärend zugestalten). Bitte beachten Sie immer die Hinweise auf den jeweiligen Bögen.
- Alle Felder eines Dokumentationsbogens müssen ausgefüllt werden
- Die ausgefüllten Bögen verbleiben komplett und zusammenhängend im Ordner.
- Monitor E.Obarcanin sammelt die CRFs bei ihren Monitoring-Besuchen ein
- Patiententagebücher, Laborbefunde, Arztbriefe, etc., welche der Dokumentation beigefügt werden sollen, müssen anonymisiert und mit der Patientennummer versehen werden. Um Vertraulichkeit zu gewährleisten, darf der Name der Versuchsperson **niemals** im Dokumentationsbogen oder irgendeinem anderen Dokument erscheinen, das dem Projektleiter zurückgegeben wird.

Fehlende Daten:

- Falls keine Antwort zutrifft, werden die betreffenden Felder durchgestrichen und daneben vermerkt: **n.a. = not applicable (nicht zutreffend)**
- Wenn etwas nicht durchgeführt wurde, werden die betreffenden Felder durchgestrichen und daneben vermerkt: **n.d. = not done (nicht durchgeführt)**
- Falls die Antwort auf die betreffenden Fragen nicht bekannt ist, werden die betreffenden Felder ebenfalls durchgestrichen und daneben vermerkt **n.k. = not known**.
- Diese sollten jedoch sparsam und möglichst nicht ohne Begründung verwendet werden.

Beispiele:
Bluglukose zum Zeitpunkt der pharmazeutischen Intervention wurde nicht durchgeführt = n.d.
Vermittlung von Kenntnissen zur Sexualität, Kontrazeption, Menstruation, Familienplanung bei Jungen mit Diabetes Typ 1= n.a.
Fehlende Angabe aus der Anamnese oder z.B.letzter Ketonwert = n.k.

Korrekturen auf CRF:

- Fehler sollen durch einzelne Linie ausgestrichen werden, so dass der ursprüngliche Eintrag lesbar bleibt. Die Korrektur wird daneben geschrieben, handschriftlich datiert und mit Initialen abgezeichnet.
- Der Gebrauch von Korrekturflüssigkeit (Tipp-Ex) oder Ähnlichem ist nicht zulässig

Datum/Unterschrift:
Datum und Unterschrift vom Prüfapotheker auf allen ausgefüllten CRFs nicht vergessen

Dokumentation von AEs und SAEs

- Unerwünschte Ereignisse (AE=adverse events) sollen in Übereinstimmung mit dem Protokoll im CRF (auf dem betreffenden Erhebungsbogen) dokumentiert werden.
- **Adverse Event (AE)**

Ein AE ist jedes nachteilige Ereignis, das einem teilnehmenden Patienten im zeitlichen Zusammenhang mit der Untersuchung widerfährt. Dieses muss nicht ursächlich im Zusammenhang mit der Untersuchung stehen. Der behandelnde Arzt (oder sein Vertreter) und Apotheker des teilnehmenden Patienten stellen fest, ob unerwünschte Ereignisse eingetreten sind und stufen diese wie folgt ein:
Leicht: Klinisches Symptom oder Zeichen, das gut toleriert wird.
Mittel: Klinisches Symptom oder Zeichen, das ausreichend ist, die normale Aktivität zu beeinträchtigen.

DIADEMA study data flow (brief manual) (continued)

Schwer: Klinisches Symptom oder Zeichen, das zu einer starken Beeinträchtigung der normalen Aktivität oder zur Arbeitsunfähigkeit oder der Unfähigkeit, alltägliche Verrichtungen durchzuführen, führt.

➢ Im Falle eines schwerwiegenden unerwünschten Ereignisses (SAE = Serious adverse event) muss innerhalb von 24 Stunden per Telefon oder Telefax Verbindung mit dem Leiter der Untersuchung aufgenommen werden:

Frau Prof. Dr. med. Stephanie Läer
Institut für Klinische Pharmazie und Pharmakotherapie
Heinrich-Heine-Universität Düsseldorf
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☎ +49 211 - 81-10740 +49 211 - 81-10741
stephanie.laeer@uni-duesseldorf.de

SAE (Serious Adverse Event)
Ein SAE ist jede Reaktion oder Nebenwirkung, die ein deutliches Risiko oder eine Gefahr für den Patienten darstellt. Dieses muss nicht ursächlich im Zusammenhang mit der Untersuchung stehen. Als SAE gilt jedes medizinische Ereignis, das

- ➢ zum Tode führt oder lebensbedrohlich ist
- ➢ zur Krankenhausaufnahme führt
- ➢ zu bleibenden oder erheblichen Schäden oder zu Invalidität führt
- ➢ jedes andere Ereignis, dass ein vergleichbares Kriterium erfüllt.

Attachment 7: Physician case report form

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

CASE REPORT FORM (DOCTOR)

Date of Birth: _____ / _____ (MM.JJ) Age: _____ Gender: Male □ Female □

Diagnosis of diabetes: Type 1 ☐ Type 2 ☐ Other type ☐ _____
Date of first diagnosis: _____ / _____ / _____ Diabetes Duration: ___ Years

Size: ____ cm Weight: ____ kg ____ BMI _____kg / m²

Last HbA1c _____ in percent (%)

Blood Pressure: ___ / ___ mmHg
Total cholesterol / HDL / LDL_____ / _____ / _____ / mmol / l Quarter, year: _____
Triglycerides: _____ mg / dl Quarter, year: _____

Albumin: _____ mg / l or ____ mg/24 Quarter, year: _____

DKA during 6 months study period: Yes ☐ No ☐

Severe Hypoglycemia in the last month: Yes ☐ No ☐ Number: _____

Total Insulin Dose ____ I.U./day

Blood Glucose (random) _____ mmol/l

Is there evidence of renal dysfunction? yes ☐ no ☐

Increased or decreased laboratory data in the last 3 months (quarter, year):

_____

_____

_____

Known drug allergies or adverse drug reactions:

_____

_____

Other diagnoses

_____

Signature (Physician)_____**Diabetes educator :** _____ **Date :**

Attachment 8: Pharmacist case report form

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

CASE REPORT FORM (PHARMACIST)

1. CLINICAL INFORMATION

Blood Glucose Testing: yes ☐ no ☐

Blood Glucose Diary (written/ electronic): yes ☐ no☐

Blood Glucose Diary : Last Week ☐ Last 24 hours ☐

Number of BG-Testing per day ____

Time of BG-Testing:

On an empty stomach ☐ Before meal ☐ 2 hours after meal ☐ Bedtime ☐ At night ☐

Morning Blood Glucose: ____ mmol/l Date : _____

Blood Glucose at the time of pharmaceutical intervention _____mmol/l

Hypoglycemia* in the last month: yes ☐ no ☐ Number: ____

(BG Diary, Records of BG Testing Device)

* Blood Glucose of 50mg/dl or 2.8 mmol/l with hypoglycemic symptoms)

Number of severe Hypoglycemia with third party assistance in the last month: _____

* (Study outcomes)

Ketone measurement (blood or urine) if BG more than >250mg/dl, 13.89 mmol/l:

yes ☐ no ☐

Last Ketone value : _____ Date :_____

Signature (Pharmacist) : _____ Date :

Pharmacist case report form (continued)

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

2. INSULIN USE

Insulin Pump ☐ Pen ☐ Other ☐

Total daily Insulin Dose: ____ I.U

Total daily Dose Basal Insulin: ____ I.U.

Total daily Dose fast/rapid acting Insulin (Bolus): ___I/U

Insulin injection per day: ___

Number of bolus doses (Pump) per day : ____

Insulin used: NPH ☐ Levemir ☐ Lantus ☐ Novolog ☐ Humalog ☐ Novorapid ☐

☐ Regular ☐ Other _____

Adherence with insulin therapy: ☐ yes ☐ no

Problems: _____

_____

_____

Reasons for Non-Adherence_____

_____

_____

Correct Insulin Application: ☐ yes ☐ no

Comments: _____

Side effects of Insulin therapy: ☐ yes ☐ no

If yes, specify _____

Interaction Insulin and other medication ☐ yes ☐ no if yes, specify

_____

Other medication used:

_____

Signature (Pharmacist) : _____ **Date :**

Pharmacist case report form (continued)

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.□□□ Date □□.□□.□□□□ Visit □

3. LIFESTYLE /NUTRITION

Regular physical activity/Sport: ☐ yes ☐ no

Insulin dose adjustment to sport: ☐ yes ☐ no

Problems: _____

_____

_____

Adherence to nutrition recommendation /CH counting: ☐ yes ☐ no

Problems: _____

_____

_____

Signature (Pharmacist) : _____ **Date :**

Attachment 9: Pharmaceutical care plan

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

PHARMACEUTICAL CARE PLAN

ASSESSMENT/INDIVIDUAL GOALS

1.
2.
3.
4.
5.
6.
7.

PHARMACEUTICAL CARE PLAN (until next visit)

1.
2.
3.
4.
5.
6.
7.

Please discuss this plan with doctor/diabetologist (Visits 3 and 6)

Plan discussed: ☐ **yes** ☐ **no** Signature Dr. (diabetologist): _____

Signature (Pharmacist) _____ **Date :**

Pharmaceutical care plan (continued)

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

ADDITIONAL COMMENTS (PCP):

_____
_____
_____
_____

_____
_____
_____
_____

_____
_____
_____

Please discuss this plan with doctor/diabetologist (Visits 3 and 6)

Plan discussed: □ yes □ no Signature Dr. (diabetologist): _____

Signature (Pharmacist): _____ Date:

Attachment 10: Patient satisfaction questionnaire

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.□□□ Date □□.□□.□□□□ Visit □

QUESTIONNAIRE: SATISFACTION WITH PHARMACEUTICAL CARE

Fill this page in at visit 3 and 6

					
1. **How satisfied are you with the pharmaceutical care?**	1	2	3	4	5
2. **How satisfied are you with the accessibility of the clinical pharmacist?**	1	2	3	4	5
3. **How satisfied are you with the time your study pharmacist takes for you?**	1	2	3	4	5
4. **How satisfied are you with eduction on insulin action in relation to physical activity and carbohydrate intake?**	1	2	3	4	5
5. **How satisfied are you with the education about insulin dosage and application, other therapies and possible side effects and interactions of insulin and other medications by your study pharmacist?**	1	2	3	4	5
6. **Could you discuss your questions, about your individual treatment goals, based on the treatment guidelines with the study pharmacist to your satisfaction?**	1	2	3	4	5
7. **Would the service "pharmaceutical care" help improve your blood glucose levels persistently if they were offered, for example in a public pharmacy or a pharmacist in the hospital?**	1	2	3	4	5

Attachment 11: Patient WHO-5 Wellbeing questionnaire

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.□□□ Date □□.□□.□□□□ Visit □

WHO (FIVE) WELLBEING INDEX
Fill this page in at Visits 1, 3, and 6

Over the last two weeks	All the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1. I have felt cheerful and in good spirits	5	4	3	2	1	0
2. I have felt calm and relaxed	5	4	3	2	1	0
3. I have felt active and vigorous	5	4	3	2	1	0
4. I woke up feeling fresh and rested	5	4	3	2	1	0
5. My daily life has been filled with things that interest me	5	4	3	2	1	0

Attachment 12: Drug-related problems

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

DRUG RELATED PROBLEMS

1. Elevated blood sugar levels (hyperglycemia) ☐ yes ☐ no

2. Hypoglycemia ☐ yes ☐ no

3. Additional BG measurements required ☐ yes ☐ no

4. Adverse effect (insulin) ☐ yes ☐ no

Please specify: _____

5. Effective dosage form available (insulin) ☐ yes ☐ no

6. Patient does not want to take insulin ☐ yes ☐ no

7. Patient does not understand the instructions ☐ yes ☐ no

8. Other: _____

Attachment 13: Adherence to guidelines

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.□□□ Date □□.□□.□□□□ Visit □

ADHERENCE WITH SELECTED GUIDELINES (adapted from ISPAD and DDG)

Fill this page in at Visits 1, 3, and 6

1. An individual plan for frequency and intervention, blood glucose levels, insulin doses (mode, time, dose calculation),meals, symptoms and management of hypo- and hyperglycemia should be created **for schools** Yes □ No □ Quarter, year : ____

2.**Bloodglucose testing** should be done at least 4 times a day □ Yes □ No

3.**The target HbA1c** should be ≤ 7.5 % without occurance of severe hypoglycemia. Blood glucose fluctuations should be minimized. Yes □ No □

4. Determination of HbA1c for monitoring metabolic control should be done at least every three months. Yes □ No □ Quarter, year : _____

5.Ophtalmologist control should take place once a year

Yes □ No □ Quarter, year : _____

6.**Screeining for nephropathy** should take place once a year

Yes □ No □ Quarter, year : _____

7.Blood pressure should be determined every 3 months, but can be measured at least once a year Yes □ No □ Quarter, year : _____

8. Lipid screening should take place every 2 years

Yes □ No □ Quarter, year : _____

9.Neuropathy screening should take place annually

Yes □ No □ Quarter, year : _____

10. Immunization, especially influenza and pneumococcal vaccination for children with type 1 diabetes Yes □ No □ Quarter, year : _____

11.Sick Day Management protocol should be created

Yes □ No □ Quarter, year : _____

12.**Urin or blood ketones** are to be determined during episodes of uncontrolled hyperglycemia, insulin deficiency , illness or impending ketoacidosis

Yes □ No □ Quarter, year : _____

Attachment 14: Educational contents during pharmaceutical care visits

DIADEMA STUDY: CASE REPORT FORM Pharmaceutical Care of adolescents with T1DM

Patient Nr.☐☐☐ Date ☐☐.☐☐.☐☐☐☐ Visit ☐

1. Evaluation of individual treatment goals based on the treatment guidelines
Done: Yes □ No □ Date _____

2. Teaching the basing of insulin therapy and practical skills for performing the insulin therapy
Done: Yes □ No □ Date _____

3.Skills training for independent adjustment of insulin
Done : Yes □ No □ Date _____

4.Learning of self-control measures and their documentation and interpretation
Done : Yes □ No □ Date _____

5.Detection, treatment and prevention of acute complications (hypoglycemia, hyperglycemia, infections, etc.)
Done : Yes □ No □ Date _____

6.Theoretical knowledge and practical skills regarding the effect of physical activity on blood glucose regulation
Done : Yes □ No □ Date _____

7.Training of problem solving strategies for special situations
Done : Yes □ No □ Date _____

8.Imparting knowledge about sexuality, contraception, menstruation, family planning
Done : Yes □ No □ Date _____

9.Dealing with possible tobacco, alcohol and / or drug use;
Done: Yes □ No □ Date _____

10.Information about check-ups
Done : Yes □ No □ Date _____

9. Partial Publication of this Thesis

Parts of this thesis are in the process of being published and have been presented at a conference.

Research paper:

Obarcanin E, Krüger M, Müller P, Nemitz V, Hasanbegovic S, Kalajdzisalihovic S, Schwender H, Läer S. Pharmaceutical care of adolescents with type 1 diabetes mellitus: a randomized, controlled trial. Revised manuscript submitted to the International Journal of Clincial Pharmacy (IJCP) on September 22, 2014. Manuscript Nr. IJCP-D-14-00322R1

Oral presentation with abstract:

Obarcanin E, Krüger M, Läer S. Pharmaceutical care of adolescents with T1DM, DIADEMA study. Presented at the German Diabetes Society (DDG) 49th Annual Symposium, Berlin, Germany, June 2014.

X. Curriculum Vitae

Emina Obarcanin

Education

October 2006 – August 2009	*Working Professional Doctor of Pharmacy (PharmD) Program, University of Florida, Gainesville, USA*
January 2002	*Third State Exam in Pharmacy Studies, Düsseldorf, Germany*
October 1996 – September 2000	*Pharmacy studies at Heinrich-Heine University, Düsseldorf, Germany*
November 1992 – June 1996	*Suitbertus Gymnasium (A level), Düsseldorf, Germany*

Practical training

August 2008 – September 2008	*University of Florida Health Shands Hospital (Clinical clerkship), Internal Medicine ward, Gainesville, USA*
December 2000 – May 2001	*Practical Year in the community pharmacy: Schadow Pharmacy, Düsseldorf, Germany*
June 2001– December 2001	*Practical year in the pharmaceutical Industry (Analytics department) WALA/Dr. Hauschka Bad Boll, Germany*

XI. Contributions and Funding

The DIADEMA was a clinical study with two study sites with numerous study staff who contributed to the study protocol, data collection and analysis.

Contribution to the study: Emina Obarcanin and Prof. Dr. med. Stephanie Läer contributed to the conception and design of the DIADEMA study. In addition to Emina Obarcanin and Prof. Dr. med. Stephanie Läer, Dr. Snijezana Hasanbegovic and pharmacist Manfred Krüger gave their input to the DIADEMA study protocol.

Diabetes educators Verena Nemitz (Germany) and Sena Kalajdzisalihovic (Bosnia-Herzegovina) collected and entered clinical data: HbA1c, triglycerides, total cholesterol, HDL, LDL, DKA, age, sex, BMI, BG, duration of diabetes, blood pressure, insulin dose, insulin delivery device, number of severe and non-severe hypoglycemia and number of BG tests/ day from the intervention and control groups patients. Emina Obarcanin and 14 other study pharmacists performed all Pharmaceutical Care visits and collected data such as BG, hypoglycemia, insulin use, ketone measurement and data on DRP, satisfaction with PhC, WHO (5) Wellbeing index and adherence to selected guidelines from the intervention group patients. Emina Obarcanin performed clinical data monitoring at the end of the study and consolidated all collected clinical data and questionnaires scores.

Prof. Dr. Holger Schwender performed the statistical analysis of the clinical data collected by diabetes educators as well as the statistical analysis of the questionnaires collected by Emina Obarcanin and other pharmacists.

Emina Obarcanin, Prof. Dr. med. Stephanie Läer, Manfred Krüger, Dr. Snijezana Hasanbegovic, Dr. Petra Müller, Sena Kalajdzisalihovic, Verena Nemitz and Prof. Dr. Holger Schwender performed data analysis and interpretation.

Funding: For the duration of the DIADEMA study including the conceptual and planning phase, Emina Obarcanin was financially supported by the Deutsche Akademische Austauschdienst (DAAD), the Lesmüller Stiftung, and the Heinrich-Heine University, Düsseldorf, Germany. The study was partially supported by the Lesmüller Stiftung.

XII. Acknowledgements

My dissertation has been a hard and long journey. However, I would have not gotten so far without the generous support of my advisor, colleagues, and family.

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I am very grateful to pediatric diabetologists: Dr. Snijezana Hasanbegovic for her suggestions, and constructive criticism, and Dr. Petra Müller for her openness and endorsement to conduct this study and to diabetes educators: Verena Nemitz and Sena Kalajdzisalihovic for their extraordinary support with the study. I thank the directors of the pediatric clinics, Prof. Dr. Tim Niehues and Prof. Dr. Senka Mesihovic-Dinarevic and all participating pharmacists and patients of the DIADEMA study.

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Also, I am very thankful to my friend Zumreta Galijasevic, whose personal story and positive attitude inspired me to start working with adolescents with T1DM.

Lastly, I would like to thank my family for all their love and encouragement My heartfelt thanks to my parents for raising me with a love for medicine, especially to my mother Dr. Razija Ajanovic, who always supported me in all my pursuits. I would like to thank Monika Sölch for her support and gentle presence since my school days, and for helping me make the best decision to study pharmacy. I would like to thank my supportive and encouraging husband, Denis Obarcanin, for his endorsement and patience, especially in the final phase of my dissertation. Most of all, I thank my children, Arno and Emma, for being an unfailing source of love and inspiration.

XIII. Erklärung zur Dissertation (Declaration to the Dissertation)

Hiermit erkläre ich, Emina Obarcanin, an Eides statt, dass ich die Dissertation mit dem Titel:

”Pharmaceutical Care of Adolescents with Type 1 Diabetes Mellitus:

DIADEMA Trial: A Randomized Controlled Trial”

selbständig und ohne unzulässige fremde Hilfe unter Beachtung der “Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf” verfasst habe. Andere als die von mir angegebenen Quellen und Hilfsmittel habe ich nicht benutzt. Die Dissertation wurde in der vorgelegten oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf den Emina Obarcanin