Paediatric Heart Failure Pharmacotherapy: a Europe-wide Survey Study and a Delphi Process

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I. Erklärung zur Dissertation

Ich versichere an Eides statt, dass die Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der "Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf" erstellt worden ist. 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 Cristina Castro Díez

II. Danksagung

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III. Zusammenfassung

Pharmakotherapeutische Strategien zur Behandlung einer Herzinsuffizienz bei Kindern werden bei fehlender pädiatrischer Evidenz durch die Extrapolation von Daten aus Erwachsenenstudien und eigene Erfahrungen unterstützt. Spezifische Kriterien für eine optimale Verwendung von Angiotensin-Converting Enzym Inhibitoren (ACE-I) in dieser Population sind nicht etabliert und über die häufig routinemäßig verwendeten Arzneimitteltherapien ist nicht viel bekannt. Das Ziel dieser Arbeit war die Verbesserung des Verständnisses aktueller Therapieansätze und die Schaffung einer Grundlage für die Planung weiterer Forschungen und Strategien zur Optimierung der Pharmakotherapie bei Kindern mit Herzinsuffizienz.

In einem ersten Schritt wurde eine europaweite Umfrage durgeführt, mit dem Ziel, die Pharmakotherapie der pädiatrischen chronischen Herzinsuffizienz sowie den Einsatz von ACE-I in diesem Kontext zu charakterisieren. Einhundert in der pädiatrischen Kardiologie tätige Ärzte aus 100 verschiedenen Krankenhäuser in 27 europäischen Ländern nahmen an der Umfrage teil. Therapieschematas, die den Leitlinienempfehlungen für Erwachsenen ähneln, aber auch deutliche Abweichungen wurden beobachtet. Trotz einiger Zurückhaltung bei Neugeborenen, scheinen ACE-I ein wichtiger Teil der Behandlungsstrategie der Herzinsuffizienz bei Kindern zu sein. Die Anwendung bei Kindern mit singulärem Ventrikel erfolgt häufig, was im Gegensatz zur derzeitigen pädiatrischen Evidenz steht. Unterschiedliche Anwendungskriterien und eine mögliche herstellungsbedingte Variabilität deuten darauf hin, dass signifikante Unterschiede im Risiko-Nutzen-Verhältnis für Kinder bestehen können. In einem zweiten Schritt wurden ausgewählte kontroverse Aspekte in einem Delphi-Prozess von einem internationalen Expertengremium, bestehend aus 13 pädiatrischen Kardiologen, diskutiert. Das Ziel bestand darin, die qualifizierte Experten zusammenzuführen, einen Konsens zu ermöglichen und Übereinstimmungen sowie Unstimmigkeiten zu identifizieren.

Zusammenfassend bietet diese Arbeit relevante Einblicke in die alltägliche Praxis der Pharmakotherapie der pädiatrischen Herzinsuffizienz und führt zu einem Konsens qualifizierter Kinderärzte hinsichtlich der Bedeutung verschiedener Aspekte, die für die Standardisierung der Therapie relevant sind, sowie hinsichtlich der Angemessenheit spezifischer Therapieneinstellungen.

IV. Summary

In the absence of conclusive paediatric evidence, pharmacotherapeutic strategies for the management of heart failure in children are largely supported by adults' data extrapolation and own experience. Great uncertainty exists regarding optimal use of angiotensin-converting enzyme inhibitors (ACE-I) in this population and little is known about commonly used drug treatment routines. The aim of this thesis was to enhance understanding of current therapeutic approaches and provide a basis to help plan further research and strategies to optimise pharmacotherapy in heart failure children.

In a first step a Europe-wide survey study was conducted with the aim of characterising paediatric heart failure maintenance pharmacotherapy and investigating how ACE-I are used in this setting. Out of 200-eligible, 100 physicians dedicated to paediatric cardiology representing 100 hospitals in 27 European countries participated. Drug regimens consistent with adults' evidence and marked deviations were observed. Despite some reluctance to use them in newborns, ACE-I seem key in paediatric heart failure treatment strategies. Use in single ventricle patients seems frequent, in apparent contradiction with current paediatric evidence. Disparate usage criteria and potential formulation-induced variability suggest significant differences may exist in the risk-benefit profile children are exposed to. In a second step, controversial aspects identified were discussed in a Delphi process among an international expert panel of 13 paediatric cardiology physicians. The aim was to maximise the potential of qualified opinion, facilitate consensus and highlight areas of agreement and disagreement.

In summary, this thesis provides relevant insight into real-life everyday practice of the pharmacotherapy of paediatric heart failure and shows consensus of qualified paediatricians on the importance of a set of topics relevant to the standardisation of therapy as well as on the appropriateness of specific therapeutic attitudes.

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ACE-I	Angiotensin-converting enzyme inhibitor
CHD	Congenital heart defects
CI	Confidence interval
CNP	Comparison not possible
CSV	Comma-separated value file format
DCM	Dilated cardiomyopathy
EMA	European Medicines Agency
EU	European Union
FP7	Seventh Framework Programme
HF	Heart failure
ID	Identification number
LENA	Labelling of Enalapril from Neonates up to Adolescents project
MCQ	Multiple choice question
NA	Not applicable
SCQ	Single choice question
SD	Standard deviation
OC	Overall consistency
ONQ	Open question requiring a numeric answer
OQ	Open question
OTQ	Open question requiring a text answer
RCT	Randomized controlled trials
WP12	Working package 12 in LENA project

IX. Motivation and aim of the thesis

Paediatric patients are often treated as small adults, but they actually represent a very special population that deserves specific consideration. Not only the aetiology and underlying pathophysiology of diseases in children are frequently different from that in adults; age and development-dependent changes that occur throughout the paediatric age affect significantly the pharmacokinetic and pharmacodynamic behaviour of medicines (Kearns et al., 2003).

Despite this, clinicians and policy makers have been forced to rely on safety and efficacy data gathered in adult trials, since children have been largely neglected in drug research and an absence of high-weighted paediatric evidence exists in most pharmacotherapy areas (Caldwell et al., 2004). In this scenario, off-label and unlicensed prescribing are by necessity a widespread practice in paediatrics. The reported percentage of children who receive at least one off-label and/or unlicensed drug during hospitalisation ranges from 42.0 to 100%; 12.2 to 70.6% of hospital paediatric prescriptions are off-label and 0.2 to 47.9% involve unlicensed drugs (Magalhães et al., 2015). This unfortunately means that medicines in paediatrics are often used without proper underlying recommendations and implies that children may be exposed to increased risks (European Medicines Agency, 2004), without a guarantee that they are going to experience therapy-related benefits.

Aiming to address this problematic, the 26th of January of 2007 entered into force the so-called Paediatric Regulation, Regulation (EC) No 1901/2006 (The European Parliament and the Council of the European Union, 2006). This law intends to "ensure that medicines for children are fully adapted to their particular needs" (EUR-Lex, 2014). Among other measures, it established European Union (EU) funding to promote research into off-patent medicines for children and an EU inventory of the paediatric therapeutic needs to focus the research (European Medicines Agency, n.d.). An Expert Group Meeting held in 2010 at the European Medicines Agency exposed the unmet needs in the development of drugs

for the therapy of paediatric heart failure and included angiotensin-converting enzyme inhibitors (ACE-Is) among the drugs to be prioritised in the research of this condition (European Medicines Agency, 2010). Responding to this demand the Seventh Framework Program EU funded project LENA "Labeling of enalapril from neonates up to adolescents" emerged. LENA aims at developing an age-appropriate solid oral formulation of enalapril suitable for the therapy of heart failure in all paediatric subsets, generating pharmacokinetic and pharmacodynamic data, collecting safety data and providing evidence-based paediatric dose recommendations. The present thesis has been conducted in the context of this project.

It has been observed that existing prescribing habits may affect the viability of research and the extent to which new paediatric evidence is integrated into daily practice (Li et al., 2011; Zak et al., 2017). Since commonly used paediatric heart failure drug treatment routines across Europe were mostly unknown, gaining a better understanding about established prescribing practices seemed of great interest to place LENA and future research into the right context. With this purpose, a Europe-wide survey study was conducted (**Chapters 2** and **3**). Subsequently, areas of controversy identified were discussed in a Delphi process among a panel of paediatricians with expertise in this field (**Chapter 4**). In the absence of solid evidence, expert's opinions can be a valuable contribution to enable decisions to be made when evidence is scarce or contradictory. The aim was to maximise the potential of qualified opinion and ultimately contribute to advancing the goal of safe and effective heart failure pharmacotherapy in children.

Chapter 1

Pharmacotherapeutic management of paediatric heart failure: a European survey part 1

1.1 Introduction and aim

Paediatric heart failure is a complex syndrome that englobes a variety of aetiologies and clinical presentations. Agreeing on a standard definition has been challenging, but Hsu and Pearson (2009) proposed paediatric heart failure can be referred to as "a progressive clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular abnormalities that results in characteristic signs and symptoms including oedema, respiratory distress, growth failure, and exercise intolerance, and accompanied by circulatory, neurohormonal, and molecular derangements."

Despite its low incidence, paediatric heart failure is an important public health concern due to its economic and social impact (Hsu and Pearson, 2009). No comprehensive epidemiological data exist, but it has been estimated that 14-18 per 100 000 children are hospitalized each year due to heart failure (Rossano et al., 2012), accounting for 10% to 33% of all paediatric cardiac admissions (Sommers et al., 2005; Massin et al., 2008). Children whose hospitalization is complicated by heart failure can have a >20-fold increase in the risk of death (Rossano et al., 2012).

Unlike in adults, ischemic heart diseases are rarely the underlying cause. Congenital heart defects (CHD) are responsible for most cases diagnosed in developed countries, even though the majority are resolved with surgery (Sommers et al., 2005). Broadly, CHD leading to heart failure can be divided into volume overloading lesions, among which left-to right shunt lesions and valve regurgitation are the main types, pressure overloading lesions and complex CHD, where single ventricle physiology is a prominent type (Hsu and Pearson, 2009). Dilated cardiomyopathies (DCM) are the main cause of heart failure in patients with structurally normal hearts (Sommers et al., 2005; Massin et al., 2008) and account for 60%

of paediatric cardiac transplants in Europe (Rossano et al., 2016). Interest in drug therapy has increased especially with the goal of keeping patients stable until cardiac transplant or surgery can be performed, and/or to delay or avoid the need (Rossano and Shaddy, 2014a).

Beneficial effects of pharmacotherapy for adult heart failure are well established. Different neurohumoral antagonists have shown to impact the disease prognosis and among them (ACE-I) are the only drugs recommended by both European and American adults heart failure guidelines for all patients (Yancy et al., 2013; Ponikowski et al., 2016). However, the efficacy of these medicines in children has yet to be confirmed. Evidence in paediatrics comes mainly from heterogeneous observational and small experimental studies, whilst the only two published large randomized controlled trials (RCT) failed to prove benefit of the drugs under study (Shaddy et al., 2007; Hsu et al., 2010). Whether potential differences between adult and paediatric heart failure or study design issues are responsible for those findings remains controversial (Bajcetic et al., 2014; Rossano and Shaddy, 2014b). In the absence of conclusive data, paediatric therapeutic strategies are largely supported by adults' data extrapolation and own expertise (Kantor et al., 2013; Kirk et al., 2014). Little is known about commonly used drug treatment routines.

This study was conducted with the aim of characterising heart failure pharmacotherapy for children across Europe, with special focus on ACE-I use. This would enable a better understanding of current therapeutic approaches to be elucidated and disseminated and highlight areas requiring further knowledge. In this chapter, results on the role of ACE-I according to underlying cardiac disease and heart failure maintenance drug therapy are presented.

1.2 Methods

1.2.1 Overall study design

A web-based survey type study design was selected to provide the best opportunity to collect information from a wide range of participants where resources of time, staff and budget were limited. Electronic circulation had the advantage of enabling the questions to be distributed quickly to a large yet targeted geographically disperse population. Previous relevant surveys were reviewed and recommendations published in survey research and questionnaire design best practice guidelines followed (Eysenbach, 2004; Burns et al., 2008; Draugalis et al., 2008; Vogt and Läer, 2011; Andres, 2012). Thirteen experts with specialised knowledge in different aspects relevant to the study design supported the various steps. The detailed process for the survey and survey instrument design and its distribution to participants is described in **Figure 1.1**.

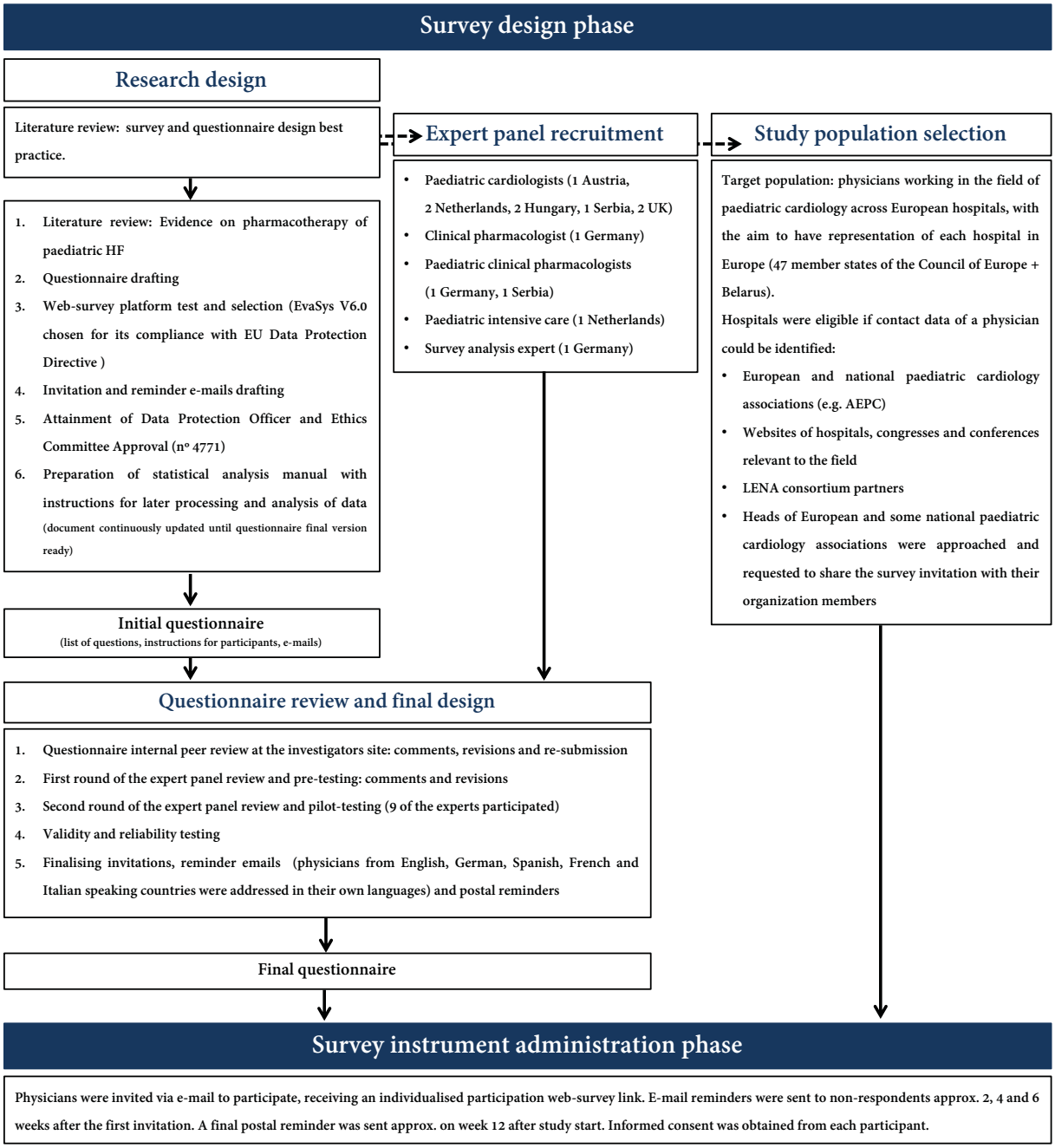


Figure 1.1 Survey and survey instrument design and administration
This figure is an adaptation of that published by Vogt and Läer (2011).

1.2.2 Survey instrument development and description

Questionnaire topics were selected from the results of a literature review and expert group discussions. The survey was peer reviewed at the investigators site and pre- and pilot-tested by members of the expert panel and reliability and validity were assessed (Burns et al., 2008; Andres, 2012) with positive results (**Appendix A**). The resulting questionnaire (**Appendix B**) explored usage patterns of ACE-I and drug therapy for DCM-related heart failure. Demographic questions about survey participants were also included.

Questionnaire was designed to be completed within 15 minutes (Andres, 2012) and contained single choice, multiple choice and open questions. Routing filters were implemented; hence participants were presented only those questions that according to their own answers were applicable to them. A minimum of 12 questions and maximum of 23 questions (47 if considering sub-questions) displayed to each participant. An overview of the questionnaire routing can be seen in **Appendix C**.

1.2.3 Study participants

The target population was physicians providing paediatric cardiology care in hospitals across Europe, with the aim to have representation of each hospital. The 47 member states of the council of Europe and Belarus were considered (48 countries targeted). Hospitals were eligible if contact data of at least one clinician dedicated to the field of paediatric cardiology were available. Since no official registries exist, a non-probability sampling design was deemed acceptable (Andres, 2012). Centres and physicians' contact data were identified through European and national paediatric cardiology association websites and presidents, hospital and cardiology conferences websites and LENA (https://www.lena-med.eu) consortium partners. Where contact data of more than one paediatrician in a hospital were identified, the one that seemed more related to the management of heart failure patients was invited to participate.

1.2.4 Survey instrument administration

Web-survey platform EvaSys® v. 6.0 was used for the administration of the questionnaire. This was selected for its compliance with EU Data Protection Directive 95/46/EC. An invitation e-mail, containing an individualised survey participation link, was sent to each physician. Subjects from English, German, Spanish, French and Italian speaking countries were addressed in their own languages. Instructions to facilitate the navigation through the web-questionnaire were provided. Approximately 2, 4 and 6 weeks after the first invitation, non-respondents received e-mail reminders and a final postal reminder was sent on week 12 after study start. Copies of invitation and reminders are provided in **Appendix D**.

1.2.5 Data collection and statistical analysis

Data were collected between January and May 2015. A manual providing detailed work instructions for the management and analysis of the data was prepared (**Appendix E**). To minimise errors during data processing, data extraction from the EvaSys® web-survey platform and preparation of ready-to-analyse data were conducted by two researchers independently, and results were checked for consistency. A copy of the filled-in and signed checklists used to this end is provided in **Appendix F**. Data analysis was performed using R® v.3.2.1 and R-Studio® version 099.465. Descriptive statistics were used. Charts presented were created in Excel® v.16.10.

Response rate was calculated as the number of different hospitals from which at least one physician submitted a completed or partially completed questionnaire divided by the number of different hospitals from which a physician was sent the invitation with questionnaire link. If more than one physician in a hospital answered, the first questionnaire received was taken into consideration for analysis. Hospitals were excluded from the analysis if the clinician contacted expressed his wish not to

participate, did not feel able to participate because of limited experience, was retired or the completed questionnaire was returned after the pre-established deadline.

1.2.6 Ethical conduct of the study

This study was conducted according to the ethical principles that are outlined in the Declaration of Helsinki and in compliance with EU Data Protection Directive 95/46/EC. A data protection procedure plan description (*Verfahrensverzeichnis*[1]) was elaborated in order to comply with the requirements of the North Rhine-Westphalia Data Protection law (**Appendix G**[2]). Study was approved by the Heinrich-Heine-University Düsseldorf Institutional Data Protection Officer and Ethics Committee (**Appendices H**[2] **and I**[2] respectively). Electronic informed consent was obtained from each participant; a sample is provided in **Appendix J**.

[1] Since the study was conducted in Düsseldorf, it was mandatory to comply with the requirements of the North Rhine-Westphalia Data Protection law, harmonised with German Data Protection Law (BDSG) and EU Data Protection Directive 95/46/EC. According to BDSG, every state or private body that deals with personal data must document how these are to be handled in order to guarantee that individual rights are protected. *Verfahrensverzeichnis* is the term that has been established in BDSG to refer to this documentation.

[2] Document in original German version.

1.3 Results

1.3.1 Survey participants

Physicians representing 204 different hospitals in 39 countries were invited to participate, of whom 200 were considered for the analysis and 4 were excluded according to the pre-established criteria. The survey achieved an overall response rate of 50% (100/200). Physicians from 27 different countries in the four European regions participated (**Figure 1.2**). Most of them were working in a paediatric cardiology unit (91%) with over five years work experience in this field (96%). Participants' demographic data are presented in **Table 1.1**. As shown in **Figure 1.3**, 70% of participants considered pharmacotherapy to have an impact of between 6 and 8 points out of 10 on the course of the disease; 82% selected scores ≥ 6.

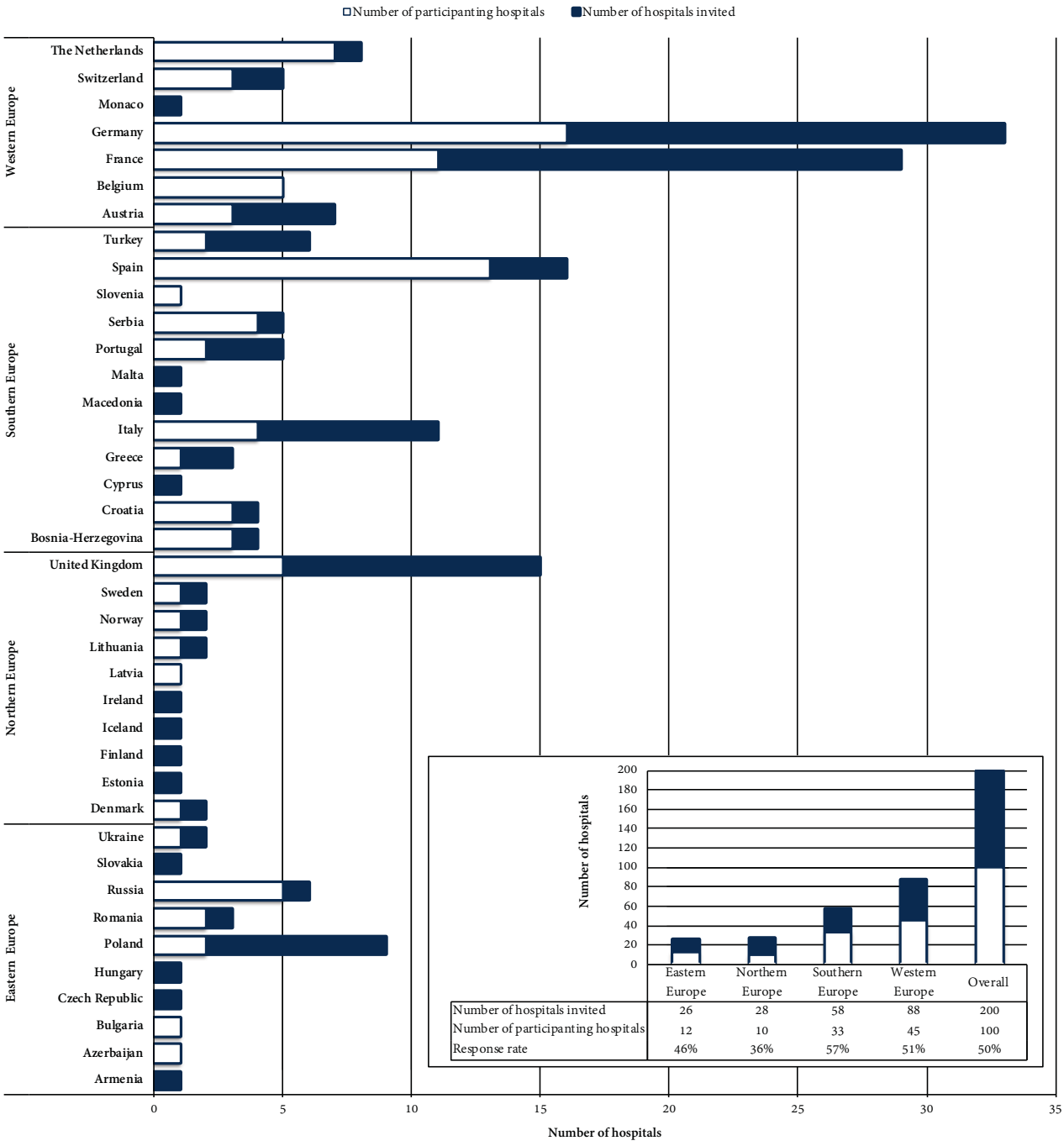


Figure 1.2 Survey participation by country and region

Contact data of physicians from 204 different hospitals in 39 European countries could be found. Four were excluded from analysis: 1 physician contacted expressed his wish not to participate, 1 did not feel able to participate because of limited experience, 1 was retired and 1 returned the completed questionnaire after the pre-established deadline. Criteria of the United Nations statistical division for Europe (United Nations Secretariat, Statistics Division, n.d.) were followed for the classification of countries by European region. Four of the countries referred to are not considered as being European in this classification. Armenia and Azerbaijan were assigned here to Eastern Europe, Cyprus and Turkey to Southern Europe.

Table 1.1 Demographic characteristics of the participants

Experience in paediatric cardiology	**n/total**	**%**
<1 year	0/100	0
1-5 years	4/100	4
> 5-10 years	13/100	13
> 10 years	83/100	83
Type of working unit	**n/total**	**%**
Paediatric cardiology	91/100	91
Paediatric critical care	3/100	3
Neonatology	1/100	1
Other	5/100	5
Total number of paediatric beds in the working hospital	**n/total**	**%**
≤50	22/100	22
51-100	23/100	23
101-150	24/100	24
151-200	8/100	8
>200	17/100	17

Participants that selected the answer option "other" when asked about the type of unit in which they were working, reported working in a cardiology department that provides medical care also to adult patients or in a combined paediatric cardiology-critical care department. Note that 6 of the participants did not answer the question on how many paediatric beds the hospital they work in has.

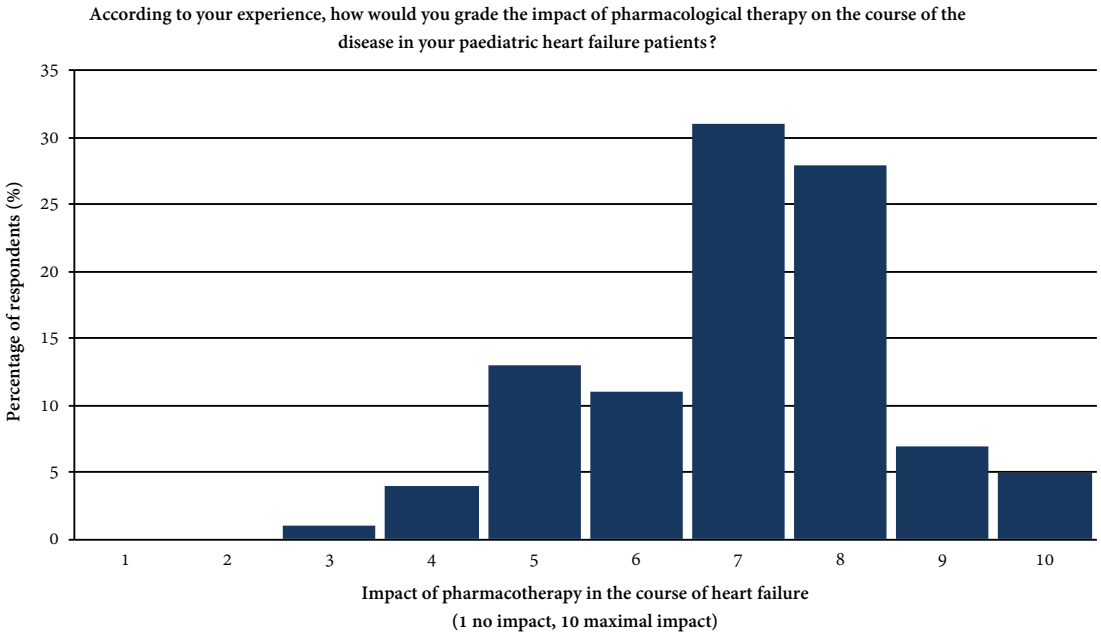


Figure 1.3 Physicians' perception on the impact of pharmacological therapy on the course of the disease in paediatric heart failure patients

1.3.2 ACE-I use in heart failure according to aetiology: DCM and CHD

All participants reported using ACE-I therapy for cardiac diseases associated with heart failure development; 100% when DCM is the underlying cause and 97% in the context of CHD. **Figure 1.4** shows the responses of the later 97 participants on ACE-I use within four types of CHD according to heart failure symptomatic state. Most of those physicians agreed on the usefulness of the therapy with ACE-I in patients with left-to-right shunt (LRS) lesions (82%), single ventricle lesions (87%) and/or valve regurgitation (95%). A marked division of opinions existed among the physicians asked with regard to pressure overloading lesions (45% yes versus 51% no). Twelve participants reported using ACE-I for other CHD (mainly systemic right ventricle, Marfan syndrome, post-surgical correction of aortic coarctation, complex CHD).

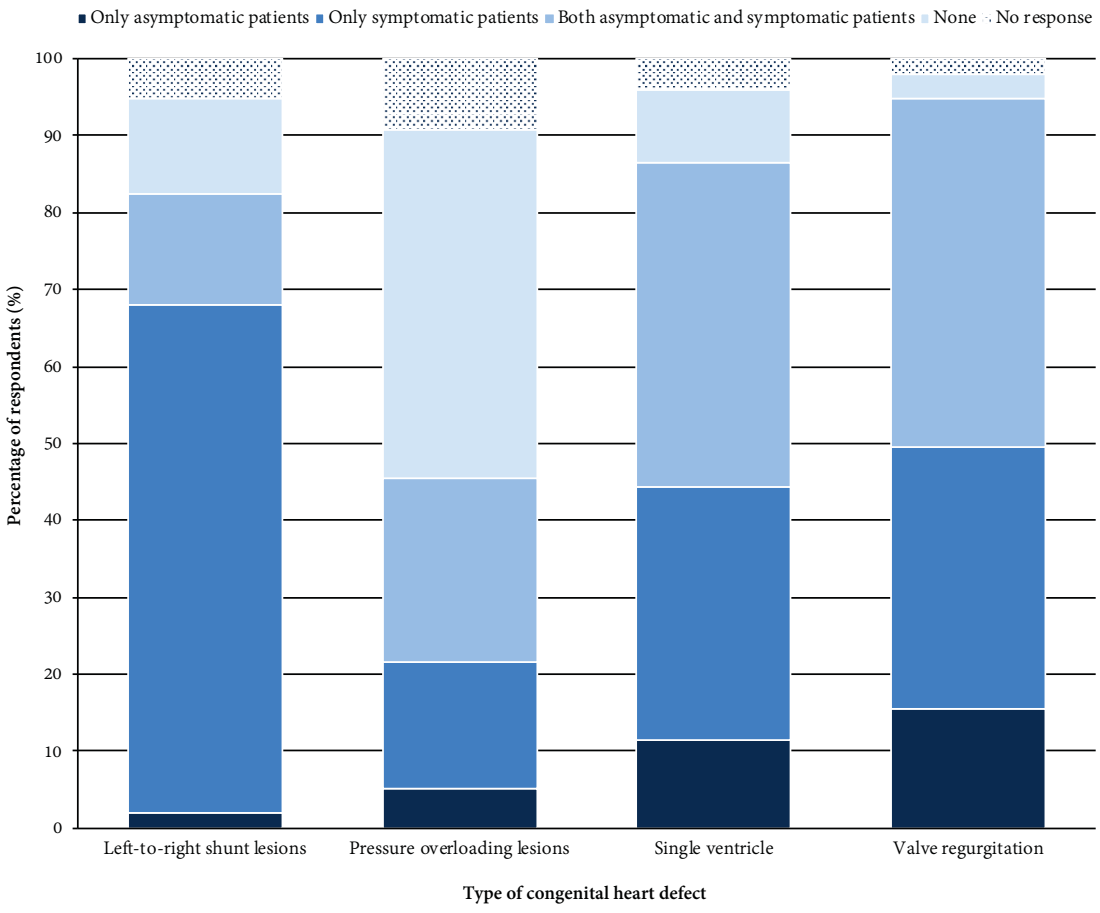


Figure 1.4 ACE-I use for the management of congenital heart defects
This question was applicable to 97 participants (n total for percentage calculation).

Eighty percent of these 97 physicians reported using ACE-I in patients with CHD after heart surgery. The duration of treatment varied, with the majority (64%) using them for a period of between 1 and 6 months. Only 7% use ACE-I for more than 6 months (**Table 1.2**).

Table 1.2 ACE-I use in patients with congenital heart defects after heart surgery

Post-surgery time	n/total	%
< 1 month	9/97	9
1 to 3 months	34/97	35
>3 months to 6 months	28/97	29
>6 months	7/97	7
No use after surgery	16/97	16

Note that 3 of the 97 participants to whom this question was applicable did not answer it.

1.3.3 Drug regimens for the management of heart failure due to DCM - symptomatic patients

Table 1.3 provides participants' responses to questions regarding drugs introduced as initial therapy for DCM heart failure patients who are not dependent on inotropic drugs, and medication introduced as add-on therapy where patients remain symptomatic. Twenty-five different drug combinations were reported to be used for initial therapy (**Table 1.4**). Thiazide and/or loop diuretics are part of the drug regimens reported by 83% of the participants. Seventy-nine percent recorded that they start treatment with a drug regimen that includes an ACE-I and a diuretic (thiazide and/or loop diuretic), whilst 61% initiate treatment with a combination that includes an ACE-I and an aldosterone antagonist, and 53% select a combination that includes all three. Forty-four percent of participants that start with beta-blocker, while 52% use beta-blockers as add-on therapy to treat patients that remain symptomatic. Fifty-four participants use cardiac glycosides, most of them (39) as add-on therapy.

Table 1.3 Report on drug use in stable, symptomatic heart failure related to dilated cardiomyopathy

	Initial therapy		**Add-on therapy**		Duplicate answers		**Overall total**	
Drug class	**n/total**	**%**	**n/total**	**%**	n/total	%	**n/total**	**%**
ACE-I	96/100	96	9/100	9	5/100	5	100/100	100*
Angiotensin receptor blocker	2/100	2	8/100	8	1/100	1	9/100	9
Beta-blocker	44/100	44	52/100	52	5/100	5	91/100	91
Loop diuretic	76/100	76	19/100	19	3/100	3	92/100	92
Thiazide diuretic	14/100	14	21/100	21	2/100	2	33/100	33
Aldosterone antagonist	65/100	65	27/100	27	4/100	4	88/100	88
Cardiac glycoside	16/100	16	39/100	39	1/100	1	54/100	54
Other	2/100	2	6/100	6	0/100	0	-	-

The results corresponding to two multiple-choice questions are presented, one referring to initial therapy and one referring to add-on therapy prescribed for patients that remain symptomatic despite initial therapy. Some of the participants gave a duplicate answer, as they selected the same drug class in both questions; number of participants that did so for each drug class are shown in column "duplicate answers". The total number of physicians that reported prescribing each drug class for the therapy of DCM-related symptomatic heart failure is presented under column "overall total". Drugs reported under "other" were acetylsalicylic acid and ivabradine for initial therapy and ivabradine and intravenous inotropes for add-on therapy.

*Please note, even though 100% of the participants reported using ACE-I as therapy for symptomatic DCM-related heart failure, either as initial or add-on therapy, only 95% of the participants selected the answer option DCM in question 1, when asked "Which cardiac diseases related to heart failure development do you manage with ACE-I?". This means 5 of the participating physicians did not provide consistent answers in this regard.

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DCM, dilated cardiomyopathy.

Table 1.4 Drug regimens used as the initial therapy of stable symptomatic heart failure related to dilated cardiomyopathy

Drug combinations	n/total	%
Single-drug regimen		
ACE-I	5/100	5
Two-drug regimen		
ACE-I + Aldosterone antagonist	1/100	1
ACE-I + Beta-blocker	4/100	4
ACE-I + Loop diuretic	12/100	12
ACE-I + Thiazide diuretic	1/100	1
Aldosterone antagonist + Loop diuretic	2/100	2
Three-drug regimen		
ACE-I + Aldosterone antagonist + Beta-blocker	4/100	4
ACE-I + Aldosterone antagonist + Loop diuretic	20/100	20
ACE-I + Aldosterone antagonist + Thiazide diuretic	1/100	1
ACE-I + Aldosterone antagonist + Cardiac glycoside	3/100	3
ACE-I + Beta-blocker + Loop diuretic	7/100	7
ACE-I + Beta-blocker + Thiazide diuretic	1/100	1
ACE-I + Cardiac glycoside + Loop diuretic	4/100	4
Aldosterone antagonist + Loop diuretic + Thiazide	1/100	1
Four-drug regimen		
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic	14/100	14
ACE-I + Aldosterone antagonist + Beta-blocker + Thiazide diuretic	4/100	4
ACE-I + Aldosterone antagonist + Loop diuretic + Cardiac glycoside	3/100	3
ACE-I + Aldosterone antagonist + Loop diuretic + Thiazide diuretic	1/100	1
ACE-I + ARB + Loop diuretic + Cardiac glycoside	1/100	1
Aldosterone antagonist + Beta-blocker + Cardiac glycoside + Loop diuretic	1/100	1
Five-drug regimen		
ACE-I + Aldosterone antagonist + Beta-blocker + Cardiac glycoside + Loop diuretic	3/100	3
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic + Thiazide diuretic	4/100	4
ACE-I + Aldosterone antagonist + Cardiac glycoside + Loop diuretic + Acetylsalicylic acid	1/100	1
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic + Ivabradine	1/100	1
Six-drug regimen		
ACE-I + Aldosterone antagonist + ARB + Beta-blocker + Loop diuretic + Thiazide diuretic	1/100	1

Most of the participants start with 2 (20%), 3 (41%) or 4 (24%) drugs in combination. One third of participants (34%) reported starting with a drug combination that includes 4 or more drugs.

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

1.3.4 Drug regimens for the management of heart failure due to DCM - asymptomatic patients

Most of the participants (89%) reported considering pharmacotherapy for asymptomatic patients with DCM (either always, 66%, or under certain circumstances, 23%). Ninety-one percent of them reported using ACE-I in this situation, with 29% as monotherapy. Fifty-five percent of these participants deemed it appropriate to prescribe beta-blockers, 29% as a two-drug only combination with an ACE-I. Twenty-eight percent prescribe aldosterone antagonists to asymptomatic patients; 21% thiazide and/or loop diuretics. Detailed information is displayed in **Tables 1.5** and **1.6**.

Table 1.5 Drugs used for asymptomatic heart failure related to dilated cardiomyopathy

Drug class	n/total	%
ACE-I	81/89	91
ARB	6/89	7
Beta-blockers	49/89	55
Loop Diuretic	17/89	19
Thiazide Diuretic	6/89	7
Aldosterone antagonists	25/89	28
Cardiac glycosides	2/89	2
Other	1/89	1

This was a multiple-choice question. Note that one of the 89 participants that reported using drug therapy for patients with asymptomatic heart failure due to dilated cardiomyopathy did not answer this question. Acetylsalicylic acid was the drug reported under "other".
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Table 1.6 Drug regimens used for the therapy of asymptomatic heart failure related to dilated cardiomyopathy

Drug combinations	n/total	%
Single-drug regimen		
ACE-I	26/89	29
Aldosterone antagonist	1/89	1
Beta-blocker	3/89	3
Two-drug regimen		
ACE-I + Aldosterone antagonist	3/89	3
ACE-I + ARB	1/89	1
ACE-I + Beta-blocker	26/89	29
ACE-I + Loop diuretic	3/89	3
Aldosterone antagonist + Loop diuretic	2/89	2
Beta-blocker + Thiazide diuretic	1/89	1
Three-drug regimen		
ACE-I + ARB + Beta-blocker	2/89	2
ACE-I + Aldosterone antagonist + Beta-blocker	5/89	6
ACE-I + Aldosterone antagonist + Loop diuretic	2/89	2
Four-drug regimen		
ACE-I + Aldosterone antagonist + ARB + Beta-blocker	1/89	1
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic	3/89	3
ACE-I + Aldosterone antagonist + Beta-blocker + Thiazide diuretic	1/89	1
ACE-I + Aldosterone antagonist + Beta-blocker + Cardiac glycoside	1/89	1
ACE-I + Aldosterone antagonist + Loop diuretic + Thiazide diuretic	1/89	1
ACE-I + Beta-blocker + Loop diuretic + Acetylsalicylic acid	1/89	1
Five-drug regimen		
ACE-I + Aldosterone antagonist + ARB + Beta-blocker + Loop diuretic	1/89	1
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic + Cardiac glycoside	1/89	1
ACE-I + Aldosterone antagonist + Beta-blocker + Loop diuretic + Thiazide diuretic	2/89	2
Six-drug regimen		
ACE-I + Aldosterone antagonist + ARB + Beta-blocker + Loop diuretic + Thiazide diuretic	1/89	1

Note that one of the 89 participants that reported using drug therapy for patients with asymptomatic heart failure due to dilated cardiomyopathy did not answer this question. Most of the participants start with two drugs in combination (40%) or with a single drug (34%).

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

1.4 Discussion

This survey offers an overview of drug prescribing patterns for paediatric heart failure management in Europe. Pharmacotherapy seems to have become an integral part of medical care in this setting and 82% of the participating physicians consider it to have an impact ≥ 6 out of 10 points on the course of the disease, suggesting positive outcomes are being made in everyday practice.

1.4.1 ACE-I use in heart failure by aetiology: DCM and CHD

ACE-I appear to be a crucial part of treatment strategies, with all survey participants agreeing on their appropriateness for children with heart failure when DCM and/or CHD are the underlying causes. ACE-I have proven to reduce mortality and hospitalizations in adult heart failure patients (CONSENSUS Trial Study Group, 1987; SOLVD Investigators et al., 1992, 1991) having become cornerstones of therapy in this population (Yancy et al., 2013; Ponikowski et al., 2016). In DCM children, benefits in humoral and haemodynamic parameters have been documented (Stern et al., 1990; Bengur et al., 1991; Eronen et al., 1991; Seguchi et al., 1992), but only few improvements in clinical terms (Lewis and Chabot, 1993; Kantor et al., 2010). However, it is widely accepted that "DCM is the cause of paediatric heart failure that is most similar to that in adults" and thus, the assumption that benefits of the same drug therapy also apply. In line with this, paediatric guidelines recommend using ACE-I in children with symptomatic and asymptomatic ventricular dysfunction (Kantor et al., 2013; Kirk et al., 2014). The results suggest this is indeed an extended practice across Europe; all participants agree in prescribing ACE-I for symptomatic DCM patients. Of the physicians that treat asymptomatic patients, 91% also rely on ACE-I.

Virtually all physicians (97%) claimed to use ACE-I in the context of CHD. These children represent a very heterogeneous group where the origin of heart failure is very often not limited to ventricular dysfunction (Hsu and Pearson, 2009), with the extrapolation of adult data becoming more complex. Only few specific recommendations on drug therapy in children with underlying CHD have

been published (Kirk et al., 2014). Results suggest that European paediatricians believe that ACE-I play an important role in the therapy of valve regurgitation, LRS lesions, single ventricle physiology and also in the post-surgical setting, for which 80% claimed to prescribe them. Seventy-eight of the 80 participants that reported using ACE-I in LRS lesions prescribe them when patients are symptomatic. Studies on ACE-I in children with this type of CHD have conflicting results, but those that measured positive effects generally included only patients with large LRS and/or severe heart failure (Shaw et al., 1988; Frenneaux et al., 1989; Sluysmans et al., 1992). Regarding valve regurgitation, 92 physicians reported using ACE-I. Haemodynamic benefits have been described in small experimental studies that included only asymptomatic children (Alehan and Ozkutlu, 1998; Calabrò et al., 1999; Mori et al., 2000). However, most of the participants (77) considered symptomatic patients to also benefit from therapy. The 87% who report prescribing ACE-I for patients with single ventricle physiology is perhaps the most surprising finding. This appears to contrast with the conclusions of the authors of the only published large RCT in this patient group who considered their results did "not support the routine use of enalapril" (Hsu et al., 2010). A US Pediatric Heart Network survey (Zak et al., 2017) revealed that, even though a significant change in clinical practice according to this trial seemed to have occurred, 22% of physicians consulted were not familiar with the results and 28% of those who were aware did not change decisions accordingly, mainly due to disagreement with study design and interpretation of findings. These might have been also the reasons behind survey participants' responses. Overall study observations suggest reliance on evidence in adults has a strong influence regarding decisions on ACE-I use in children with CHD.

1.4.2 Therapeutic schemes for heart failure due to DCM - symptomatic and asymptomatic patients

When inquiring about the therapeutic strategies adopted when treating heart failure, it was focused on DCM-related aetiology to define a more homogeneous scenario. Twenty-five different drug

combinations for initial therapy were reported, reflecting a lack of uniformity. However, 96% of participants agreed on the appropriateness of starting with ACE-I and 83% prescribe loop and/or thiazide diuretics; 79% start with a drug regimen that combines both. These observations are consistent with current paediatric guidelines (Kantor et al., 2013; Kirk et al., 2014), which largely resemble those that have been developed for adults (Yancy et al., 2013; Ponikowski et al., 2016). In contrast, a large percentage of the participants have a criterion on aldosterone antagonists use that differs from these recommendations, as 65% include them as starting therapy. Evidence in adults (no paediatric data exist) supports the use of low-dose aldosterone antagonists in patients that remain symptomatic despite initial therapy, to reduce mortality and hospitalizations. It can be speculated that, rather than for their potential to influence prognosis, aldosterone antagonists are often introduced in paediatrics for their potassium sparing diuretic effect. However, it should be noted that Terano *et al.* (2016) found concomitant use of spironolactone to be an independent risk factor for acute kidney injury in heart failure children on ACE-I, a practice reported by 61 of those participants. Regarding beta-blockers, 91% of the participants prescribe them to treat symptomatic patients, but 52% reserve them for add-on therapy. In the only published large RCT on beta-blockers in paediatric heart failure (Shaddy et al., 2007), carvedilol did not significantly improve clinical outcomes. However, a Cochrane review of 2016 (Alabed et al., 2016) concluded that despite insufficient evidence, existing data suggest that children with congestive heart failure might benefit from them. Paediatric guidelines (Kantor et al., 2013; Kirk et al., 2014) consider beta-blocker use, but recommendations are less stringent ("might be initiated", "is reasonable to consider"). The results of the present study seem to reflect a cautious attitude. Fifty-four participants reported using cardiac glycosides, most of them (39) as an add-on drug. Digoxin has historically been the mainstay of heart failure therapy, but no systematic data in children with structurally normal hearts have been published, and agreement currently exists on their only limited role in adults (Yancy et al., 2013;

Ponikowski et al., 2016). While Canadian guidelines avoid recommending them (Kantor et al., 2013), the ISHLT guideline states "digoxin may be used to relieve symptoms in children" (Kirk et al., 2014). Study results suggest there is still wide perception that they are of benefit.

Drug therapy for the management of asymptomatic DCM children also seems widespread (89%). Since 83% to 90% of children affected with DCM will develop heart failure (Lipshultz et al., 2003; Nugent et al., 2003), interventions with the aim of delaying/preventing the worsening of the condition appears to be a particularly relevant topic. Universal agreement exists that all adults with asymptomatic left ventricular dysfunction should receive an ACE-I (Yancy et al., 2013; Ponikowski et al., 2016). Adding a beta-blocker concomitantly has proven beneficial, however advantages in adults without a history of myocardial infarction are less clear and recommendations not uniform (Yancy et al., 2013; Ponikowski et al., 2016). Twenty-nine percent of these participants stated they prescribe ACE-I monotherapy in this scenario and 29% a two-drug only combination of ACE-I and beta-blocker. While this might be justified by extrapolation from adults, the remaining 42% of physicians decide on a drug regimen that appears to not be backed up by any evidence.

1.4.3 Limitations

The survey results are constrained by the reliance on self-reported clinicians' practice (Adams et al., 1999). It was not possible to enrol a statistically representative sample and it cannot be assumed that the responses of an individual physician are consistent with practice of others from the same institution. Thus, the survey findings may not be extrapolated to standard European clinical practice. However, population characteristics (physicians representing 100 hospitals of 27 different countries and of all four European regions, 91% working in specific paediatric cardiology units and 96% with more than 5 years of experience in this field) indicate that a comprehensive picture of the current state of heart failure treatment routines has been provided.

While some inconsistent answers were identified, which suggests that the relevant questions may have been misunderstood or did not give participants the opportunity to fully express their practices, these were relatively few and with little impact on the global results. Several factors favour the quality of this study. Survey instrument development included the recruitment of a supporting expert panel, pre- and pilot-testing, reliability and validity testing with positive results, and a statistical analysis manual was elaborated for the processing and analysis of data (Burns et al., 2008; Andres, 2012).

1.5 Conclusions

The results of this survey suggest there is large reliance on pharmacotherapy for children with heart failure among European paediatricians. ACE-I seem to play a key role in treatment strategies both when DCM and CHD are the underlying cause. The apparent discrepancy between study observations and the conclusions of the Infant Single Ventricle trial (Hsu et al., 2010) are quite remarkable. Although no uniformity in the drug combinations selected for DCM-related heart failure therapy exists, in general, adult recommendations seem to have great influence on current prescribing patterns. However, aldosterone antagonists appear to be prescribed outside recommended conditions of use and there is still a great reliance on cardiac glycosides. Drug use in asymptomatic patients appears to be widespread, and a large proportion of physicians select a drug regimen not even supported by adult data.

Established prescribing practices play a critical role in the viability of further research (Li et al., 2011). The information collected provides relevant insight into real-life clinical practice, and therefore it might serve to highlight areas of controversy, help establish research priorities and strategies, and stimulate scientific collaboration to elucidate the best therapeutic options for these children. This study represents a modest but valuable contribution towards safe and efficient pharmacotherapy for the paediatric heart failure population.

Chapter 2

ACE-I in the management of paediatric heart failure: a European survey part 2

2.1 Introduction and aim

ACE-I have proven to reduce mortality and hospitalisations in adults with systolic heart failure (CONSENSUS Trial Study Group, 1987; SOLVD Investigators et al., 1992, 1991) and their role as first-line therapy is well defined (Ponikowski et al., 2016). In paediatrics, data are sparse and inconclusive but use of ACE-I in the therapy of heart failure has been recommended largely based on the assumption that similar benefits to those observed in adults may be expected (Kantor et al., 2013; Kirk et al., 2014). However, ACE-I use may necessitate off-label prescribing in this setting, which is associated with many challenges and risks (European Medicines Agency, 2004; McLay et al., 2006; Kimland and Odlind, 2012). When an ACE-I is introduced, numerous decisions must be made with regard to dosing schedules, monitoring of toxicity/effectiveness and problem solving if adverse events occur. Unlike in adults, limited practical guidance exists to support this decision-making process in paediatrics (Kantor et al., 2013; Taketomo et al., 2016). Great uncertainty exists regarding optimal use and there is ongoing concern about their toxicity profile, with severe adverse events having been described in the literature (Leversha et al., 1994; Ku et al., 2017; van der Meulen et al., 2018). Little is known about how clinicians overcome this knowledge gap in everyday practice.

In this chapter the results from survey questions aiming to describe how ACE-I are used when introduced as therapy for heart failure in paediatrics are presented. This is to enhance current understanding of their application in this condition and facilitate further discussion and research to clarify criteria to optimize their efficacy-safety profile.

2.2 Methods

Study methodology has been previously described in chapter 1 and a full copy of the distributed questionnaire provided in Appendix B.

For the analysis of reported ACE-I doses in use, where a participant entered a starting dose range, the lower limit was considered. Where a participant entered a maintenance dose range, the median value was recorded for analysis. Answers were excluded from analysis if: (1) the exact requested information (starting dose in mg/kg/dose and maintenance dose in mg/kg/day) was not provided, (2) target dose reported was smaller than starting dose or (3) the dose entered was considered not to be compatible with current knowledge (≥10 times the larger doses reported in literature for children and/or adults). Age groups were defined according to age classification for paediatric patients proposed by the European Medicines Agency (European Medicines Agency, 2001): newborns 0 to 27 days, infants and toddlers 28 days to 23 months, children 2 to 11 years and adolescents 12 years to 18 years. Data were analysed using descriptive statistics. Association between variables was statistically tested using Fisher's exact test.

2.3 Results

2.3.1 Study participants

Physicians representing 100 hospitals from 27 different countries out of the 200-eligible participated, achieving a 50% response rate. Details about study population have been provided previously (**Chapter 1**).

2.3.2 ACE-I use by age group

ACE-I were reported to be used for the management of heart failure in all paediatric age groups, although to a lesser extent in newborns compared to older age groups (**Table 2.1**). Seventy-two percent of the participants reported prescribing ACE-I in all age groups, while one fourth of participants (26%) avoid using them in the newborn population.

Table 2.1. ACE-I use by age group

Age groups	**n/total**	**%**
Newborns (0 – 27 days)	74/100	74
Infants and toddlers (28 days – 23 months)	95/100	95
Children (2 – 11 years)	99/100	99
Adolescents (12 years – 18 years)	95/100	95
Age groups (combinations)	**n/total**	**%**
All paediatric age groups	72/100	72
Infants and toddlers +Children +Adolescents	20/100	20
Newborns + Infants and toddlers +Children	2/100	2
Children + Adolescents	2/100	2
Only children	2/100	2
Infants and toddlers +Children	1/100	1
Only adolescents	1/100	1

More than one response was possible to this question.

No statistically significant association was found between the prescription of ACE-I to newborns and different variables related to the physicians or their working environment (**Table 2.2**). No country dependent pattern was observed; however, sample size was insufficient for a statistical test to be applied.

Table 2.2. Aspects potentially related to the practice of prescribing ACE-I to newborns (0 – 27 days)

Hospital size: number of paediatric beds*	**Use of ACE-I in newborns**		**p**
	No	Yes	
Small hospital (< 100 paediatric beds)	13	26	0.158
Big hospital (≥100 paediatric beds)	11	44	
Years of working experience in paediatric cardiology	**Use of ACE-I in newborns**		**p**
	No	Yes	
Short working experience ≤ 10 years	3	14	0.548
Long working experience > 10 years	23	60	
Type of ACE-I formulation in use reported	**Use of ACE-I in newborns**		**p**
	No	Yes	
Liquid formulation	11	36	0.651
Other than liquid formulations	15	38	

P values were calculated with the use of Fisher's exact test. *6 participants did not enter any response to this question. Similar results were obtained when other cut-off values were used to define big hospital (eg. ≥50 beds p = 0,559, ≥200 beds p = 0,786).

Of those participants using ACE-I within each age group, the majority selected captopril as the ACE-I of choice for newborns (73%) and infants and toddlers (66%), whilst enalapril was the most selected for children (56%) and adolescents (58%) (**Figure 2.1**). Participants' main rationale for this choice is shown in **Table 2.3**.

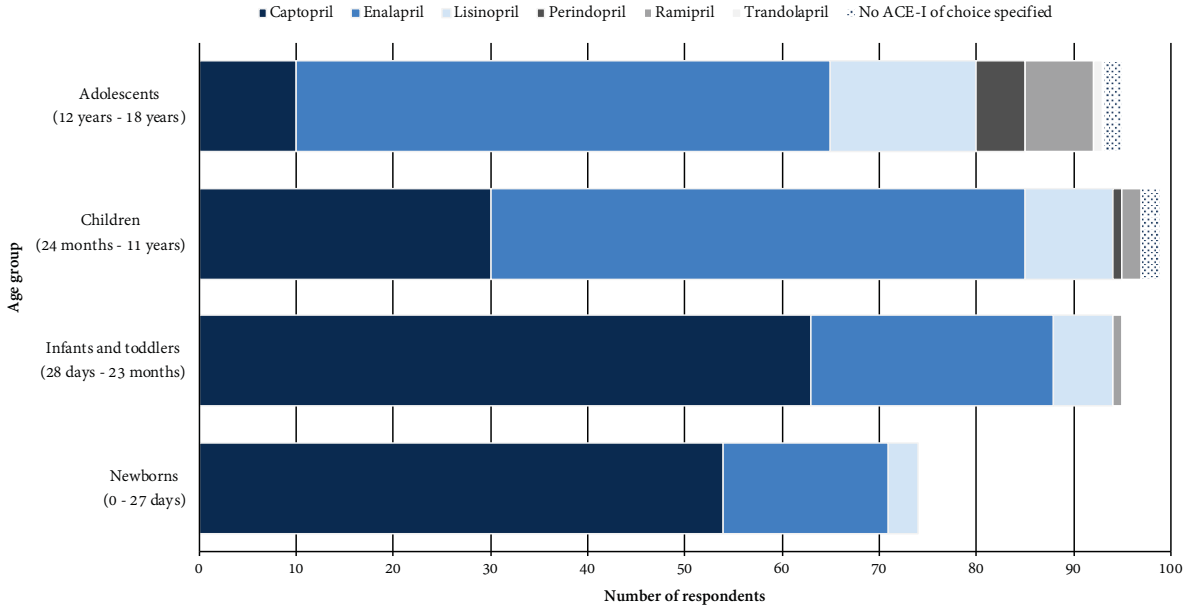


Figure 2.1 First-choice ACE-I by age group. Age groups were defined according to age classification for paediatric patients proposed by the EMA(European Medicines Agency, 2001).

Table 2.3. Rationale for first-choice ACE-I selection

Reasons	Captopril in newborns		Captopril in infants - toddlers		Enalapril in children		Enalapril in adolescents	
	n/ total	%	n/ total	%	n/ total	%	n/ total	%
More experience with use	50/54	93	55/63	87	38/55	69	43/55	78
Most appropriate formulation available	25/54	46	29/63	46	25/55	45	22/55	40
More convenient to parents/ patients	7/54	13	11/63	17	34/55	62	33/55	60
Recommended in guidelines/ books	24/54	44	29/63	46	20/55	36	22/55	40
Established in hospital protocols	25/54	46	29/63	46	16/55	29	12/55	22
No specific reason	0/54	0	0/63	0	0/55	0	1/55	2
Other	2/54	4	1/63	2	2/55	4	1/55	2

Reasons entered under "other" for captopril included "less adverse events" and "licensed for hypertension in paediatrics". For enalapril these included "2 doses", "better efficacy expected" and "less adverse events". One of the 55 participants that reported using enalapril in children did not answer this question. Age groups were defined as follows: newborns 0 to 27 days, infants and toddlers 28 days to 23 months, children 2 to 11 years and adolescents 12 years to 18 years (European Medicines Agency, 2001).

2.3.3 Starting and maintenance dose of first-choice ACE-I according to age group

A wide range of starting doses (in mg/kg/dose) and maintenance doses (in mg/kg/day) were reported for each ACE-I and age group in virtually all cases. Summary statistics of all results is provided in **Tables 2.4** and **2.5**. Results for the most commonly prescribed ACE-Is, captopril and enalapril, are presented in **Figure 2.2** and **2.3** respectively.

Table 2.4. ACE-I starting dose by age group (mg/kg/dose)

ACEI	Newborns	Infants and toddlers	Children	Adolescents
	n	n	n	n
	median (range)	median (range)	median (range)	median (range)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Captopril	**n=49**	**n=52**	**n=22**	**n=5**
	0.15 (0.01 - 1.00)	0.20 (0.03 - 1.00)	0.28 (0.05 - 1.00)	0.10 (0.10 - 0.50)
	0.22 (0.22)	0.26 (0.24)	0.33 (0.27)	0.18 (0.18)
Enalapril	**n=11**	**n=17**	**n=42**	**n=41**
	0.05 (0.005 - 0.10)	0.05 (0.02 - 0.10)	0.10 (0.01 - 0.20)	0.10 (0.01 - 0.25)
	0.06 (0.03)	0.06 (0.03)	0.08 (0.04)	0.09 (0.05)
Lisinopril	**n= 2**	**n=5**	**n=6**	**n=10**
	0.08 (0.05 - 0.10)	0.10 (0.05 - 0.10)	0.10 (0.05 - 0.20)	0.10 (0.05 - 0.30)
	0.08 (0.04)	0.08 (0.03)	0.13 (0.06)	0.13 (0.08)
Perindopril	NA	NA	**n=1**	**n=3**
			0.05	0.10 (0.05 - 0.10)
			0.05	0.08 (0.03)
Ramipril	NA	**n=1**	**n=2**	**n=5**
		0.10	0.06 (0.01 - 0.10)	0.05 (0.01 - 0.10)
		0.10	0.06 (0.06)	0.06 (0.04)

The number of participants whose answers could be taken into consideration for the calculations in each case is indicated. One participant selected trandolapril as first-choice ACE-I in adolescents, however his starting dose answer had to be excluded from analysis (dose per kg not compatible with current knowledge). NA, not applicable: an ACE-I was not selected by any participant as first-choice within a certain age group and thus, no dosage data were requested; ACE-I, angiotensin-converting enzyme inhibitors.

Table 2.5. ACE-I target/maintenance dose by age group (mg/kg/day)

ACEI	Newborns	Infants and toddlers	Children	Adolescents
	n	n	n	n
	median (range)	median (range)	median (range)	median (range)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Captopril	**n=48**	**n=54**	**n=24**	**n=6**
	1.50 (0.01 - 7.50)	2.00 (0.20 - 6.00)	2.00 (0.30 - 6.00)	1.25 (0.50 - 5.00)
	1.58 (1.23)	1.99 (1.14)	2.30 (1.56)	1.75 (1.64)
Enalapril	**n=14**	**n=21**	**n=45**	**n=44**
	0.15 (0.03 - 1.00)	0.40 (0.10 - 1.00)	0.40 (0.10 - 1.50)	0.40 (0.10 - 1.50)
	0.27 (0.29)	0.41 (0.26)	0.42 (0.32)	0.43 (0.27)
Lisinopril	**n=3**	**n=6**	**n=8**	**n=9**
	0.20 (0.20 - 0.25)	0.40 (0.20 -1.00)	0.34 (0.20 - 1.00)	0.33 (0.10 - 1.00)
	0.22 (0.03)	0.53 (0.38)	0.48 (0.34)	0.39 (0.27)
Perindopril	NA	NA	**n=1**	**n=3**
			0.08	0.13 (0.10 - 0.15)
			0.08	0.13 (0.03)
Ramipril	NA	**n=1**	**n=2**	**n=6**
		0.20	0.13 (0.05 - 0.20)	0.13 (0.05 - 0.30)
		0.20	0.13 (0.11)	0.15 (0.09)

One participant selected trandolapril as first-choice ACE-I in adolescents, however his starting dose answer had to be excluded from analysis (dose per kg not compatible with current knowledge). NA, not applicable: an ACE-I was not selected by any participant as first-choice within a certain age group and thus, no dosage data were requested; ACE-I, angiotensin-converting enzyme inhibitors.

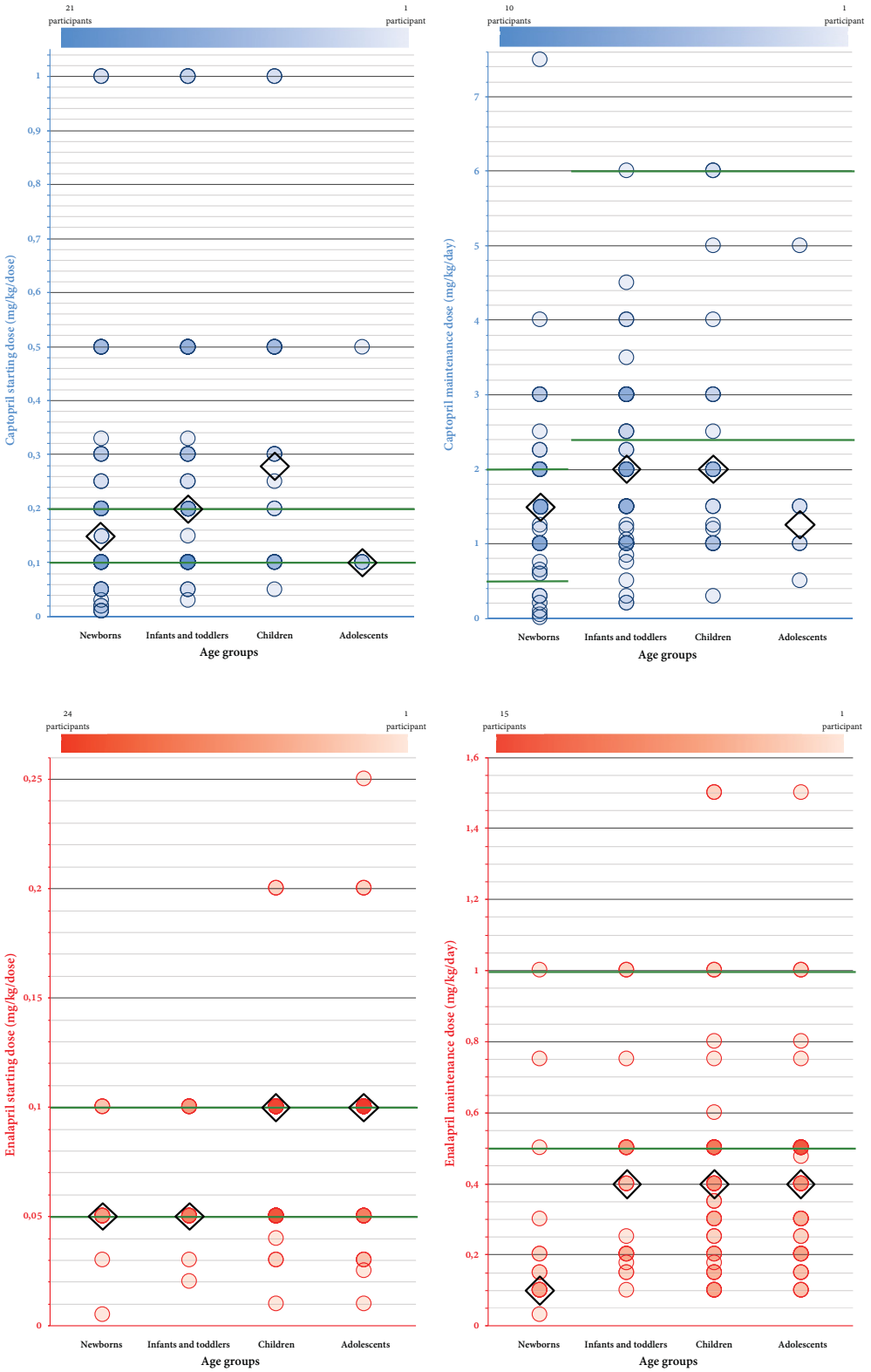


Figure 2.2 Starting dose (mg/kg/dose) and maintenance/target daily dose (mg(kg/day) in use reported by survey participants for captopril and enalapril by age group. Opacity of each point is proportional to the number of participants that entered that dose. Diamonds (◇) indicate median values. Thick green horizontal lines (—) indicate ranges of paediatric dosage recommendations that have been published (Kantor et al., 2013; Paediatric Formulary Committee, 2017; Taketomo et al., 2016). Age groups were defined as follows: newborns 0 to 27 days, infants and toddlers 28 days to 23 months, children 2 to 11 years and adolescents 12 years to 18 years (European Medicines Agency, 2001)

Dosing frequencies reported for maintenance doses for each ACE-I within each age group are presented in **Figure 2.3**. Captopril appeared to be most commonly prescribed three times per day and enalapril twice a day in all paediatric age groups except for adolescents. In this age group, the prevalence of prescribing enalapril once a day was similar to twice a day prescribing. Similarly, the percentage of clinicians reporting captopril administration two times and three times a day for adolescents was as high. Participants that reported using lisinopril, perindopril, ramipril and/or trandolapril prescribe these ACE-Is in single daily doses in virtually all cases.

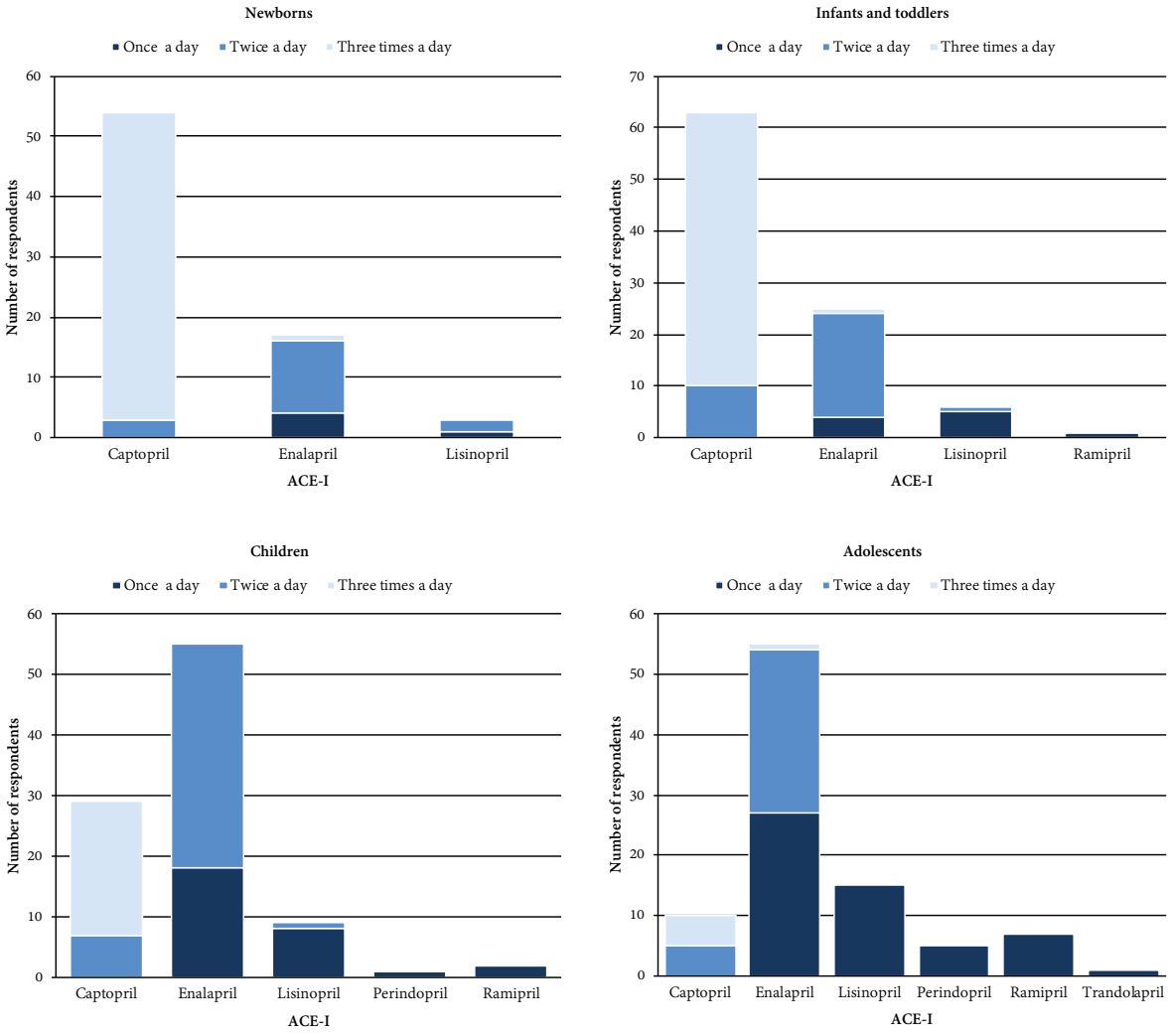


Figure 2.3 Dosing frequency of ACE-I maintenance dose reported for ACE-I of choice selected for each age group. Answer option "4 times per day" was also provided, but this was not selected in any case. One of the 30 participants that reported using captopril for children did not specify any dosing frequency.
ACE-I, angiotensin-converting enzyme inhibitors.

Division of opinions existed among the physicians surveyed on the best criterion that should be followed to establish the optimal ACE-I maintenance dose. In response to the question "Do you increase the dose of ACE-I to your target, although patient has already improved with a lower dose?" 45% of the participants answered "No", 42% "Yes" and 13% "Sometimes".

2.3.4 ACE-I effectiveness and toxicity assessment

All participants reported that they consider changes in signs and symptoms to assess the effectiveness of the ACE-I therapy. Ninety percent rely on echocardiographic or radiographic parameters. Half of the physicians reported taking into account the level of natriuretic peptide and, similarly, 54% make use of clinical scores, 55% parents' perception and 55% the need for anti-congestive medication. Only 15% reported applying quality of life scores.

In **Figure 2.4** responses of participants on their attitude towards deterioration of renal function under ACE-I therapy in terms of serum creatinine increase are displayed.

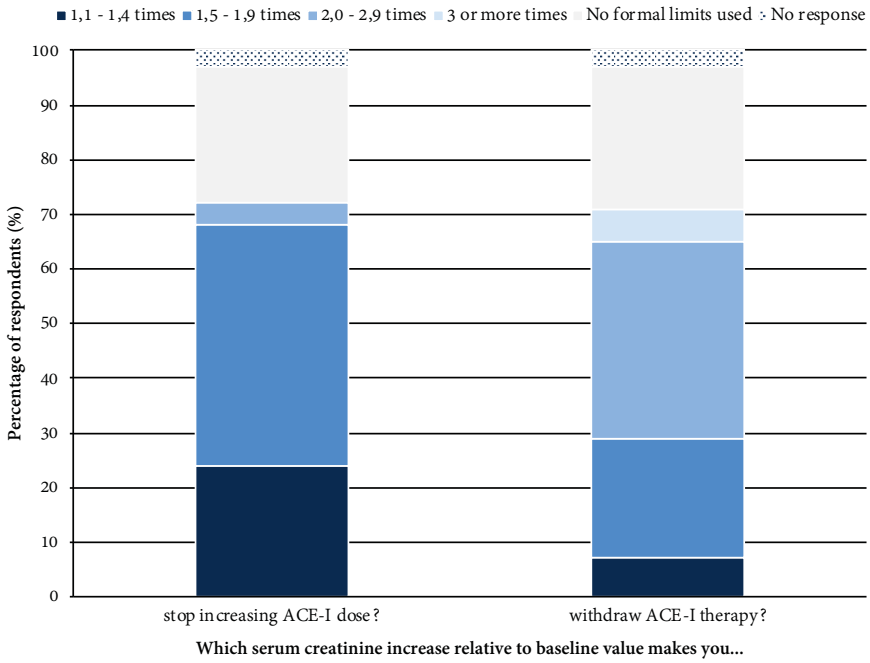


Figure 2.4 Attitude towards deterioration of renal function in terms of baseline serum creatinine level increase in the context of ACE-I therapy. The thresholds of baseline serum creatinine levels increase were based on the KDIGO proposed staging for acute kidney injury (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012) Participants were requested to select the answer that most reflected their practice

Twenty-five percent of the participants claimed not to base treatment decisions on any formal cut-off value. A rise of 1.5 to 1.9 in serum creatinine level was the most frequently selected limit as the criterion to stop increasing dose by those that reported being guided by formal limits (61%, 44 out of 72), whilst an increase of 2.0 to 2.9 times creatinine was the most frequently selected option for therapy withdrawal (51%, 36 out of 71). Regarding hypotension onset in the context of ACE-I therapy, 83% of participants reported basing the decision of stopping increasing the dose and/or withdrawing therapy on formal pre-established blood pressure cut-off values. Most of those participants (77%) use absolute blood pressure cut-off points according to age, whilst 26% consider percentage decrease in blood pressure relative to baseline value (more than one response option permitted) (**Tables 2.6** and **2.7**).

Table 2.6. If hypotension is detected, do you follow pre-established formal blood pressure limits that make you stop increasing the dose of ACE-I? Do you follow pre-established blood pressure limits that make you withdraw the therapy ACE-I?

	n/total	%
Stop increasing the dose	81/100	81
Withdraw of the therapy	29/100	29

Eighty-three participants reported following pre-established blood pressure limits in either one or both of the above scenarios. Two and 10 participants did not answer first and second question respectively.

Table 2.7. Type of blood pressure decrease limit used for decision making when up-titrating the dose of ACE-I/ What type of limit do you use?

Type of blood pressure decrease limit	n/total	%
Percentage of decrease relative to baseline value	22/83	27
Absolute blood pressure values according to age	64/83	77
Other type of limit	3/83	4

This question was applicable to all participants having reported to follow pre-established blood pressure limits in at least one of the 2 scenarios exposed in previous question (see table 2.6). One out of these 83 physicians did not answer this question. Seven participants reported using more than one type of limit when monitoring blood pressure decrease. Under "other" the following were entered: complaints, symptoms and clinical tolerance of hypotension.

2.3.5 ACE-I formulations

Forty-seven percent of the participants reported using liquid dosage forms, 44% capsules and 27% powder, when the adults' formulation is not suitable for a paediatric patient. Most of the physicians (77%) selected a single type of formulation, but 47% indicated that they relied on more than one source (hospital pharmacy, community pharmacy, prepared by parents and/or others) to supply these formulations. Detailed results are shown in **Tables 2.8** and **2.9**.

Table 2.8. Supply of ACE-I formulations prescribed when the adults' tablets are not suitable

Source	**n /total**	**%**
Provided by hospital pharmacy	66/100	66
Provided by community pharmacy	73/100	73
Prepared by parents	12/100	12
Other	2/100	2
Source (combinations)	**n /total**	**%**
Only provided by hospital pharmacy	21/100	21
Only provided by community pharmacy	28/100	28
Only prepared by parents	3/100	3
Only "other"	1/100	1
Hospital pharmacy + community pharmacy	37/100	37
Parents + hospital pharmacy	2/100	2
Parents + community pharmacy	2/100	2
Hospital pharmacy + community pharmacy + "other"	1/100	1
Parents + community pharmacy + hospital pharmacy	5/100	5

More than one response was possible to this question. "Licensed liquid formulations" was entered under "other".

Table 2.9. Types of formulations of ACE-I prescribed when the adults' tablets are not suitable

Type of formulation	**n/total**	**%**
Liquid	47/100	47
Capsules	44/100	44
Powder	27/100	27
Other	5/100	5
Type of formulation (combinations)	**n/total**	**%**
Only liquid	31/100	31
Only capsules	27/100	27
Only powder	16/100	16
Only other	3/100	3
Liquid + capsules	11/100	11
Liquid + powder	5/100	5
Powder + capsules	5/100	5
Capsules + other	1/100	1
Powder + other	1/100	1

More than one response was possible to this question. "Tablets" were entered under "other".

2.4 Discussion

The information collected in this study has advanced current understanding of the use of ACE-I in paediatrics and the results offer an insight into some of the criteria that European paediatricians apply in everyday clinical practice when using ACE-I in the therapy of children with heart failure. ACE-I appear to be used in all paediatric age groups, although almost one third of participants (26%) avoid using them in the newborn population. This is most likely due to potential variable responses to ACE-I in this age group together with low age and weight being recognised as key risk factors for renal failure in children on ACE-I (Leversha et al., 1994; Gantenbein et al., 2008; Lindle et al., 2014; Terano et al., 2016; Paediatric Formulary Committee, 2017). Some paediatric reports suggest an early introduction of therapy after heart failure onset has a positive prognostic impact (Lewis and Chabot, 1993; Kantor et al., 2010). Therefore, this finding highlights the need for guidance to allow a safe use of this drug class in the youngest population.

According to the survey results, captopril and enalapril are the main ACE-I used to treat heart failure in paediatrics. Captopril appears to be the ACE-I of choice for newborns (73%) and infants and toddlers (66%), with enalapril for children (56%) and adolescents (58%). Long-acting ACE-I (lisinopril, perindopril, ramipril and trandolapril) gain in importance as patients grow, representing 30% of the first-choices reported for adolescents. Kantor *et al.* (Kantor et al., 2013) conclude in their guideline that enalapril is an "appropriate choice for those older than the age of 2", while recommending captopril as the first-choice ACE-I in children less than 5 years old and enalapril from 5 onwards. There is currently no scientific evidence to favour any ACE-I over another by age group, however the shorter half-life of captopril might make it more flexible to use in young children. Most of the clinicians that selected captopril for younger age groups and/or enalapril for older children based their prescribing decision on experience of use. With regard to enalapril in children and adolescents, most of the clinicians agreed that

it is more convenient for use in this age group, most probably as it may be taken once a day (Taketomo et al., 2016).

The range of starting and maintenance ACE-I doses reported was wide. To what extent this variability is justified by the heterogeneity of the patients treated in the different centres, or if it is a consequence of diverging professional criteria regarding similar situations, is a question that arises from these results. Effective dosages have not yet been established in paediatric studies and doses used in reported publications are varied (Momma, 2006). Based predominantly on extrapolation from adults, starting with 0.05 to 0.1 mg/kg/dose and 0.1 to 0.2 mg/kg/dose for enalapril and captopril respectively has been recommended (Kantor et al., 2013; Taketomo et al., 2016; Paediatric Formulary Committee, 2017). Participants' reports are largely in line with or above these ranges. The British National Formulary for children (Paediatric Formulary Committee, 2017) recommends starting with 0.01 mg/kg enalapril in neonates, but survey data suggest this conservative approach is not routine practice. Roche et. al (Roche et al., 2016) found rapid ACE-I dose up-titration in paediatric patients with cardiovascular disease to be safe and advantageous. The survey results suggest observations in daily practice support this idea. In contrast, reported maintenance doses tend to be below recommendations (enalapril 0.5 to 1 mg/kg/day; captopril 0.5 to 2 mg/kg/day for neonates, 2.4 to 6 mg/kg/day for older age groups) (Kantor et al., 2013; Taketomo et al., 2016; Paediatric Formulary Committee, 2017) except for captopril in newborns. Even though these paediatric doses have not been verified, evidence in adults indicates ACE-I efficacy is closely linked to dose and an advantage of high versus low doses in terms of mortality and hospitalizations reduction seems to exist (Packer et al., 1999). Therefore, the results of the present study suggest paediatric patients might be frequently receiving potentially suboptimal doses. Perhaps poor tolerance hinders achieving high ACE-I doses in heart failure children (Hsu et al., 2010), but it is also possible that this is linked to the criterion followed to establish the optimal maintenance dose. Forty-five percent of the

participants reported they would stop up-titration once improvement had been observed in the patient. However, it appears the mechanisms that cause ACE-I long-term benefits are not relevant to symptom control (López-Sendón et al., 2004), making titration according to clinical response inappropriate in this regard. Hence, aiming towards the target doses selected in pivotal clinical trials, or failing this, towards the highest tolerated dose, is recommended in adults (Ponikowski et al., 2016). Considering an analogous approach for children would seem reasonable, but systematic data are needed to elucidate the best strategy. To note, many of the dosage responses entered by participants had to be excluded from analysis due to inconsistencies in doses or incorrect dosage units. While it is true that these might indicate a misunderstanding of the question, it is also possible that they are genuine, especially since children can be prone to medication errors, with dosing on a per kg being a key risk factor and standardisation a means of protecting children from experiencing them (The Joint Commission, 2008). This puts an additional emphasis on the need for clarifying appropriate paediatric doses.

The apparent lack of consistent and well-defined endpoints in reported paediatric heart failure studies represents a major obstacle in determining optimal dosing strategy. All physicians reported relying on their judgment regarding signs and symptoms to evaluate ACE-I therapy effectiveness. While division of opinion existed on the application of level of natriuretic peptide as a criterion (50%), 90% use cardiac imaging. The usefulness of serial echocardiography for heart failure follow-up has been recognised (Kantor et al., 2013; Kirk et al., 2014). The survey results suggest that standardising a set of relevant measurements and quantification methods to be applied in everyday practice could translate into substantial patient benefits. Only 54% of participants translate observations into severity assessment clinical scores. This may be another area of improvement since despite limitations, such scales are a means of facilitating both dialogue in daily practice and further research (Ross, 2012). Harmonizing criteria to assess response to therapy would be an important way to enable the establishment of effective

dosage, since data sharing to evaluate ACE-I therapy outcomes and interpretation of published research would be facilitated.

A similar situation applies to the evaluation of ACE-I related adverse events. Deterioration of renal function and hypotension are those most commonly reported in children with heart failure, however, clear and consistent definitions are lacking, and there are no standardised decision criteria for actions to be taken when these occur (van der Meulen et al., 2018). If a deterioration in renal function was observed in a child under ACE-I therapy, most of the physicians reported basing the decision of when to stop up-titrating and/or withdraw the therapy on formal limits (72% and 71% respectively), however no uniformity existed in the thresholds considered. The most frequently selected (1.5 to 1.9-times creatinine increase relative to baseline as the criterion to stop up-titration, and 2.0 to 2.9-times increase as the criterion to withdraw therapy) have similarities with recommendations for adults (Ponikowski et al., 2016). With regard to hypotension, 81% of the participants reported having pre-established blood pressure limits to decide when to stop increasing the dose, whilst only 29% had a fixed criterion to withdraw the therapy. This topic is complex since the approach used may change depending on patient age, comorbidities, underlying heart disease and concomitant medication. In case of hypotension, patient symptoms are most surely also determinant. Even though no clear relationship has been established between dose level and risk of adverse events (van der Meulen et al., 2018), the survey results suggest it is likely that some patients are exposed to higher risks, while others might be deprived of potential benefits due to premature dose reduction or therapy withdrawal.

A further challenge regarding dosing of ACE-I to paediatric patients is the lack of authorised age-appropriate formulations throughout Europe. The survey results imply that many patients could potentially be exposed to significant variability in dose since 47% of the respondents indicated that the ACE-I formulations they prescribe are provided by more than a single source, and 23% prescribe more

than a single type of formulation. Studies in the UK and Ireland documented that preparations used to overcome the lack of licensed medicines are heterogeneous and a variety of them with no proven bioequivalence are used interchangeably to treat children with heart failure (Mulla et al., 2007; Pabari et al., 2012). This can lead to uncertainty in the dose level achieved and hence efficacy and safety. Variability in formulations administered may also be relevant to the interpretation, comparability and validity of ACE-I safety and efficacy published data, where information on the drug formulation and its administration is often omitted.

2.4.1 Limitations

The main limitations of the present study have been discussed in **Chapter 1**. Complex topics have been addressed in a simplified manner and it was not referred to the underlying causes of heart failure in any of the questions whose results are presented here, which might influence attitude. Even though survey findings may not be fully representative of European clinical practice, population characteristics do allow us to affirm, that a good picture of the current use patterns of ACE-I in paediatric heart failure treatment in Europe has been provided.

2.5 Conclusions

The survey has shown that the use of ACE-I appears to be widespread in all age groups across Europe, although there is some reluctance to introduce them in newborns. Captopril seems to be the ACE-I of choice for young children, while enalapril seems to be preferred for older ages. Range of doses reported was wide, however it appears starting doses tend to be in line with or higher than published recommendations while maintenance doses tend to be lower. Disparate dosing criteria, potential formulation-induced variability and heterogeneity affecting criteria to define therapy outcomes, suggest that significant differences may exist in the risk-benefit profile children are exposed to. These results clearly show that there is a need for practical guidance to support decisions and that the collation and

evaluation of systematic data to provide answers should be a priority. Meanwhile, utilisation of best knowledge available should be maximised to agree on strategies and reduce unjustified variability. This study might serve as basis to determine priorities and design research and policies that enable achieving the common goal of efficient and safe use of ACE-I in children with heart failure.

Chapter 3

Pharmacotherapy in paediatric heart failure: a Delphi process

3.1 Introduction and aim

Pharmacotherapeutic strategies for the management of paediatric heart failure are largely supported by extrapolation of adult data and clinician expertise. Therefore, the prescribing of unlicensed and off-label drugs is predominant in this setting (Bajcetic et al., 2005; Kantor et al., 2013; Kirk et al., 2014). Results of the Europe-wide survey (**Chapters 1** and **2**) suggest this translates into substantial variability in clinical practice. This lack of standardization is a potential threat to the safety and quality of the medical care provided (European Medicines Agency, 2004; Kennedy et al., 2010).

It is well known that conducting randomized clinical trials in the paediatric heart failure population poses many challenges and is often not possible (Li et al., 2011; Rossano and Shaddy, 2014b). Hence it is vital to consider alternative approaches to achieve safe and effective therapy. In this regard, the potential of qualified opinion has been underused, with few structured debates and expert consensus documents having been published. However, insights of experts on an issue can be a valuable contribution for decision-making when evidence is scarce or contradictory (Jones and Hunter, 1995; Fick et al., 2003; Gurvitz et al., 2013).

The Delphi technique is a method to enable structured group discussions and has previously been used in other fields of healthcare research (Hasson et al., 2000; Fick et al., 2003; Holt et al., 2010; Keeney et al., 2011; Gurvitz et al., 2013). It is a means of "eliciting and refining group judgements" and "obtaining the most reliable consensus of opinion" (Dalkey, 1969) that is based on the assumption that group opinion is more valid than individual opinion when the issue is one where exact knowledge is not available (Keeney et al., 2011). The key features of the method are the anonymity between participants with controlled feedback provided in a structured manner (Diamond et al., 2014). It allows the inclusion

of individuals across diverse locations while minimising the main shortcomings of traditional consensus methods: the influence of dominant individuals, irrelevant communications and group pressure (Dalkey and Helmer-Hirschberg, 1962).

The aim of this study was to conduct a formal discussion, using the Delphi technique, among an expert group of paediatric cardiology physicians, on controversial aspects regarding the pharmacological management of children with heart failure which had been predominantly identified through a previous Europe-wide survey. The intention was to gain an understanding of the experts' opinions, encourage debate, facilitate consensus and highlight areas of agreement and disagreement.

3.2 Methods

3.2.1 Overall study design

The study was designed taking into consideration relevant literature on Delphi research methodology (Hasson et al., 2000; Okoli and Pawlowski, 2004; Holey et al., 2007; Hsu and Sandford, 2007; Keeney et al., 2011; Diamond et al., 2014; Häder, 2014) and publications applying this technique to health science research (Fick et al., 2003; Holt et al., 2010; Medrano López et al., 2010). A 2-round modified Delphi process design was chosen, whereby the panel of experts was given pre-selected items upon which to make a judgement (Hsu and Sandford, 2007; Keeney et al., 2011; Häder, 2014). This approach enables a greater efficiency in use of time than the traditional Delphi process, while reducing the risk of dropouts and has been used extensively by others (Fick et al., 2003; Meijer et al., 2003; Hejblum et al., 2008; Holt et al., 2010; Medrano López et al., 2010; Hamzeh et al., 2012).

3.2.2 Expert panel recruitment

The aim was to recruit an expert panel comprising 10-15 paediatricians with experience in the field of cardiology (Delbecq et al., 1975; Fick et al., 2003; Okoli and Pawlowski, 2004; Skulmoski et al., 2007; Gurvitz et al., 2013), preferably with representation of the 4 European geographical regions (United Nations Secretariat, Statistics Division, n.d.). Non-European experts were also considered. Physicians who had participated in the "European survey on the pharmacological management of paediatric heart failure" or those known by the investigators via personal contact who were considered qualified for their knowledge and interest in the topic were invited to participate via e-mail. A copy of the invitation is provided in **Appendix K**. Those invitees expressing their willingness to participate and who were available on the study dates, participated in the study and formed the expert panel.

3.2.3 Questionnaire design and administration

Recommendations on surveys and questionnaires design best practice were followed (Burns et al., 2008; Andres, 2012). Topics for discussion were predominantly selected from areas of controversy identified in the previous Europe-wide survey on the management of paediatric heart failure (**Chapters 1** and **2**). The rationale for the selection of the contents is provided in **Appendix L**. These controversial topics were framed as statements (either affirmative or negative) containing a professional judgement or a clinical recommendation on any aspect of paediatric heart failure drug therapy. Participants were asked to rate their level of agreement with the survey statements by using 5-point Likert-scales, the use of which is widely accepted (Fick et al., 2003; Lozano et al., 2008; Holt et al., 2010; Medrano López et al., 2010). Each answer category was presented with a verbal label and a numeric descriptor: 1=Strongly disagree, 2=Disagree, 3= Neither agree nor disagree, 4=Agree, 5=Strongly agree. A free text field in which participants could enter rationale and/or further comments to the answers accompanied each statement. Fourteen statements grouped under three categories were presented; Angiotensin-converting enzyme inhibitors: Considerations for optimal dosage; Angiotensin-converting enzyme inhibitors for the management of congenital heart diseases; Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy. In addition, three demographic questions were posed. The questionnaire was designed to be completed within a maximum of 30 minutes (Keeney et al., 2011). The questionnaire was peer reviewed at the investigators site. A pilot test was not deemed necessary since the questionnaire was largely based on the previously tested survey (**Chapters 1** and **2**). Furthermore, wording from recognised guidelines was adopted when possible. A potential negative impact on the later recruitment of a panel of experts of the size and motivation required was avoided.

Prior to the beginning of the study, participants received written information about Delphi methodology and guidance on how to complete the process. The web-survey platform EvaSys® version

6.1 was used for the administration of the questionnaire, which was selected for its compliance with EU Data Protection Directive 95/46/EC. An individualised link to the questionnaire was sent by e-mail together with instructions on how to navigate through the survey. In the second study round, the experts were asked to re-evaluate those statements on which consensus had not been reached after the first round. Copies of these emails are provided in **Appendix M**. Quantitative and qualitative feedback on the first round results accompanied each statement: summary of Likert-score rating, consensus evaluation and rationale provided by participants supporting their responses (Okoli and Pawlowski, 2004; Schmidt, 2007). The participants' own rating given to the statement in the previous round was not presented as part of the feedback (Häder, 2014). Additionally, the participants were provided with information (background or supporting evidence to statements) that could be relevant to facilitate the discussion. The identity of the experts in the panel remained unknown to one another throughout the study duration. A complete copy of the questionnaire can be found in **Appendix N**. The study timeline is presented in **Figure 3.1**.

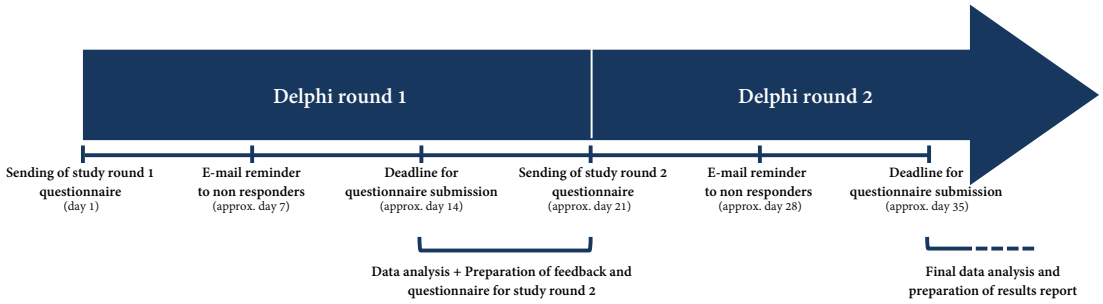


Figure 3.1 Study timeline

3.2.4 Data collection, analysis and interpretation

Data were collected between July and August 2015. A manual providing work description and instructions for the preparation, processing, and analysis of the data was developed prior to the study start (**Appendix O**). To minimise errors during data processing, data extraction from the EvaSys®

platform and preparation of ready-to-analyse data were conducted by two researchers independently, and the results were checked for consistency. Copies of the completed and signed checklists used to this end are provided in **Appendix P**. Data analysis was performed with R® version 3.2.3 and R-Studio® version 099.465. Chart presented was created in Excel® v.16.10.

The level of consensus among experts on each of the statements to be judged was evaluated by calculating the mean 5-point Likert-scale score and the corresponding 95% confidence interval (CI) after each study round. Consensus was defined as follows (Fick et al., 2003; Holt et al., 2010; Medrano López et al., 2010):

- Upper bounder of CI < 3: consensus exists among experts that a statement is false.
- Lower bounder of CI > 3: consensus exists among experts that a statement is true.
- CI includes the 3: no consensus exists among experts on whether a statement is or not true.

3.2.5 Ethics approval

This study was conducted according to the ethical principles that are outlined in the Declaration of Helsinki and in compliance with the EU Data Protection Directive 95/46/EC. A data protection procedure plan description was elaborated (**Appendix Q**[1]). Study was approved by the Heinrich-Heine-University Düsseldorf Institutional Data Protection Officer and Ethics Committee (**Appendices R**[1] and **S**[1] respectively). Electronic informed consent was obtained from each participant via EvaSys® platform; sample is provided in **Appendix T.**

[1] Document in original German version.

3.3 Results

3.3.1 Study population

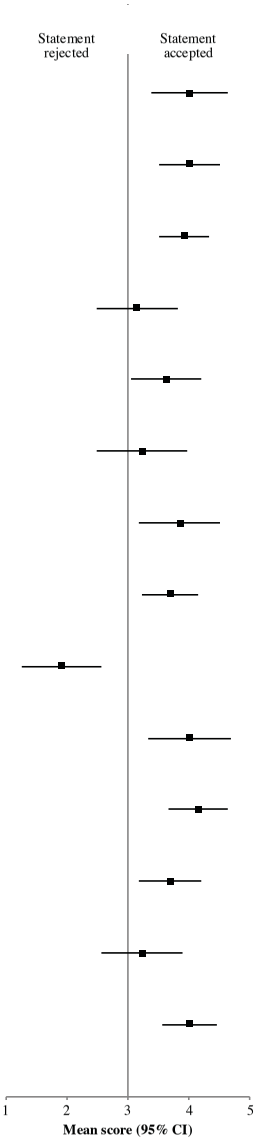
Thirty-seven paediatricians with experience in the field of cardiology were invited to participate in the study. Of the 14 that agreed to take part, one did not return the completed questionnaire within the pre-established deadline in the first study round and was therefore excluded from the study; 13 physicians completed both rounds of the Delphi process and were finally considered for analysis. Experts from Austria (1), Belgium (1), Bosnia and Herzegovina (1), France (1), Germany (3), Greece (1), Netherlands (1), Russia (1), Serbia (1), United Kingdom (1) and USA (1) participated. All four geographical regions of Europe were represented. Twelve of the 13 participants had a working experience in the field of paediatric cardiology of more than 10 years; the remaining participant had experience of between 5 and 10 years. All the physicians but one worked in a specific paediatric cardiology unit; the latter had retired but had 35 years' experience of working in a university hospital.

3.3.2 Results of the Delphi process

Overall, after the two rounds of questions agreement on 11 out of the 14 statements presented for discussion (79%) was achieved according to the pre-established criteria. In the first round of the process, consensus on 7 of the 14 statements was achieved, with six being accepted and 1 rejected. In the second study round (adapted questionnaire distributed to participants for re-evaluation of non-consensus statements can be seen in **Appendix U**) consensus on 4 further statements was achieved (all accepted). Agreement on the 3 remaining statements was not reached due to a polarisation of opinions for and against the veracity of the phrases. Detailed global results (evaluation of statements on the 5-point Likert scale and the corresponding statistics) are presented in **Table 3.1** and **Figure 3.2**.

Table 3.1. and **Figure 3.2.** Global results of Delphi process

		Statement	Evaluation on the 5-point Likert scale				Consensus (round)
			% panellist disagreeing	% panellists agreeing	Mean	(95% CI)	
ACE-I: Considerations for optimal dosage	1	There is a need for clear monitoring schedules for the early detection of acute kidney injury in paediatric patients on ACE-I therapy.	15,4	69,2	4	(3,37 – 4,63)	Yes (1)
	2	There is a need of clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.	7,7	76,9	4	(3,5 – 4,5)	Yes (1)
	3a	In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.	7,7	84,6	3,92	(3,51−4,33)	Yes (2)
	3b	In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.	46,2	46,2	3,15	(2,49-3,81)	No
	4	If deterioration of the renal function occurred in a patient on ACE-I therapy, concomitant diuretic medication should be readjusted before deciding to down titrate/ stop up-titrating the ACE-I.	15,4	76,9	3,62	(3,05-4,19)	Yes (2)
	5	If no adverse events occur, ACE-I dose should be increased to the target dose, even if the patient has already experienced improvement with a lower dose.	38,5	46,2	3,23	(2,49-3,97)	No
	6	In order to maximise the accuracy of the ACE-I dose given, the use of different types of formulations for a patient throughout the duration of the treatment should be avoided.	15,4	76,9	3,85	(3,19-4,51)	Yes (2)
ACE-I for the management of CHD	7	Paediatric patients with asymptomatic mitral or aortic regurgitation benefit from ACE-I therapy	15,4	76,9	3,69	(3,23-4,15)	Yes (2)
	8	Paediatric patients with pressure overload lesions should be routinely prescribed ACE-I.	69,2	15,4	1,92	(1,27-2,57)	Yes (1)
	9	ACE-I therapy should NOT be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction.	15,4	84,6	4	(3,33-4,67)	Yes (1)
Neurohumoral antagonists for the management of DCM-related HF	10	If beta-blockers are to be introduced for the management of heart failure, patients should also receive an ACE-I concomitantly.	7,7	84,6	4,15	(3,66-4,64)	Yes (1)
	11	Beta-blockers should be considered for the management of patients with heart failure in asymptomatic stages.	15,4	69,2	3,69	(3,18 – 4,2)	Yes (1)
	12	Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).	46,2	53,8	3,23	(2,56-3,90)	No
	13	Paediatric validated scores for heart failure severity staging should be connected with pharmacotherapeutic recommendations in further guidelines.	7,7	84,6	4	(3,56 – 4,44)	Yes (1)



Likert scale: 1=Strongly disagree, 2=Disagree, 3= Neither agree nor disagree, 4=Agree, 5=Strongly agree; ■ Mean 5-point Likert-scale score;
ACE-I, angiotensin-converting-enzyme-inhibitor; CHD, congenital heart defects; CI, confidence interval; DCM, dilated cardiomyopathy; HF, heart failure

Figure 3.3 shows the distribution of opinions in the first and second study rounds on the 4 statements upon which consensus was reached in the second study round. **Figure 3.4** shows the distribution of opinions for the 3 non-consensus statements.

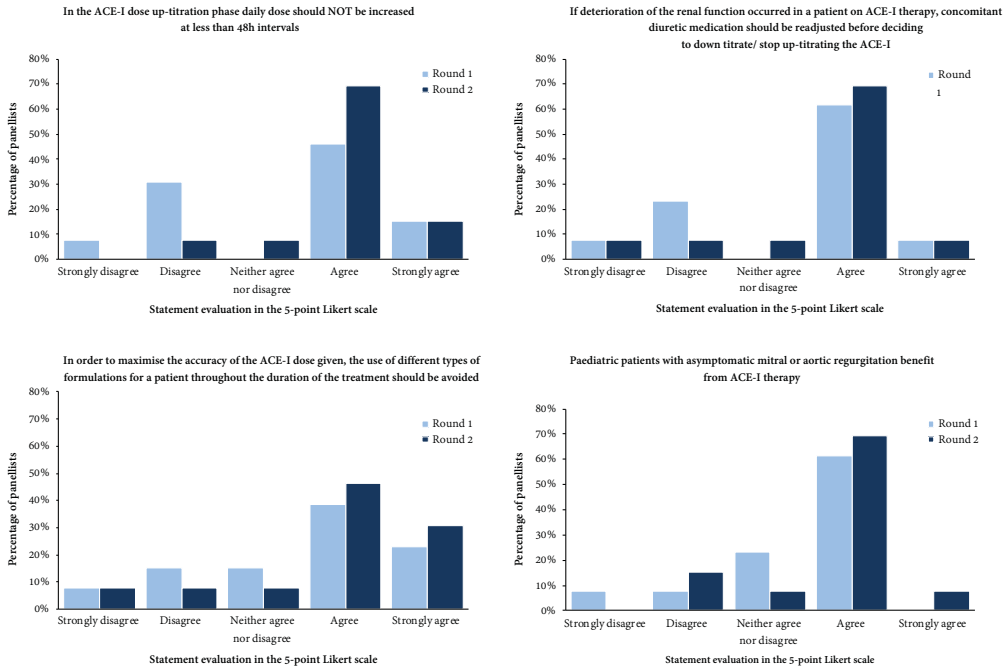


Figure 3.3. Statements upon which consensus was reached in the second study round scored in the 5-point Likert scale in the Delphi process rounds 1 and 2. ACE-I, angiotensin-converting-enzyme-inhibitor.

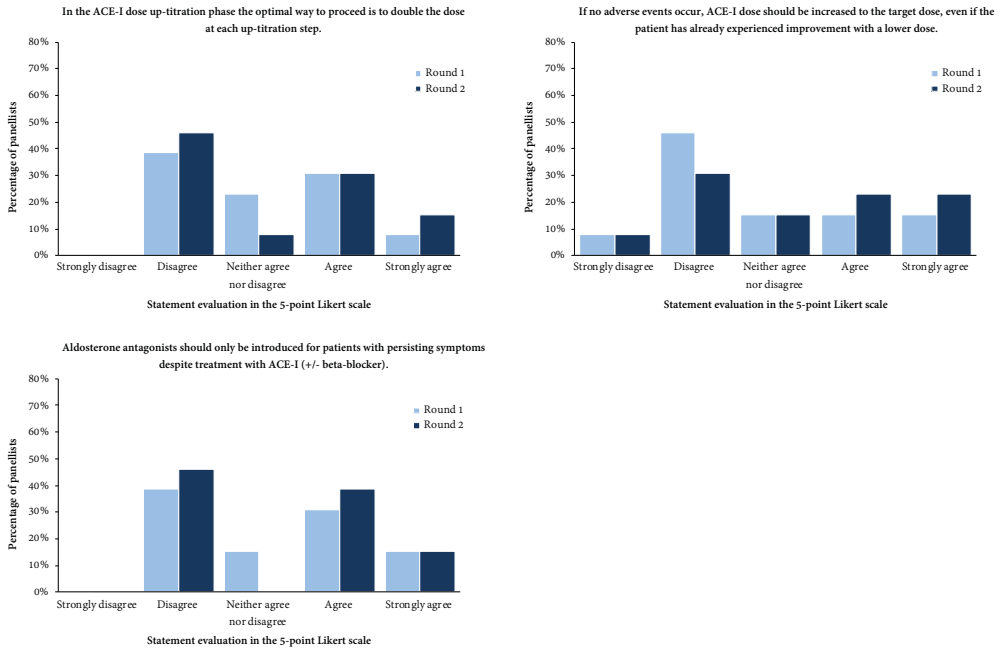


Figure 3.4. Statements upon which consensus was NOT reached in the second study round scored in the 5-point Likert scale in the Delphi process rounds 1 and 2. ACE-I, angiotensin-converting-enzyme-inhibitor.

3.4 Discussion

A series of controversial aspects relating to paediatric heart failure therapy have been discussed in this Delphi study, and the opinions of an international group of 13 physicians with experience in the field of paediatric cardiology are reflected in this document. The expert panel showed consensus in their professional judgement on 11 out of the 14 statements presented for discussion according to the pre-established criteria.

Statements upon which consensus was achieved highlight areas where closer views and common interests exist among the experts consulted. Some of those statements point to topics relevant to the standardization of the therapy that the panel agreed were of importance: developing guidance on the approach towards adverse events in the context of ACE-Is therapy, promoting the correlation of paediatric validated scores with therapeutic recommendations in further guidelines and reducing heterogeneity associated with unlicensed ACE-Is formulations.

Hypotension and deterioration of renal function are the most frequently reported adverse events related to ACE-Is in paediatric heart failure patients (van der Meulen et al., 2018). However, no standardised criteria on how to best monitor patients or define critical cut-off values exist and few specific recommendations for problem-solving when these adverse events occur have been published (Kantor et al., 2013; Taketomo et al., 2016). Results of the previous survey indicate that paediatric patients are being subjected to variable approaches for managing these aspects (**Appendix L**). The results of the Delphi process showed agreement among the expert panel in the need to fill this gap (statements 1 and 2). While it is true that current paediatric data do not allow the generation of definitive recommendations, paediatric heart failure societies and working groups may be motivated to develop guidance that compiles the best knowledge available, to facilitate a standardised approach to therapy.

Agreement was also achieved on the relevance of linking treatment algorithms to validated paediatric heart failure severity scores (statement 13), which is not yet a standard. The use of self-developed or adult-adapted grading systems is frequent (Kantor et al., 2013; Kirk et al., 2014), and it seems division of opinion exists among European paediatricians about their usefulness in everyday practice (**Appendix L**). Accurate grading of heart failure severity in children remains challenging, and paediatric-specific scoring systems that have been developed require further validation (Connolly et al., 2001; Hsu and Pearson, 2009; Ross, 2012, 2001). However, despite limitations, promoting as far as possible the use of uniform paediatric-adapted definitions seems essential to move heart failure therapy into the realm of evidence-based medicine. This would facilitate the correct application of guideline recommendations, the evaluation of therapy-related outcomes and the interpretation and performance of further research.

The results may also contribute to raising awareness of the potential consequences of the interchangeable use of different ACE-I formulations. The panel agreed on the importance of discouraging this practice (statement 6). It has been documented that unlicensed and manipulated preparations that are used to overcome the absence of licensed paediatric medicines are heterogeneous and may not be bioequivalent (Mulla et al., 2007; Pabari et al., 2012). Inconsistency in the rate and extent of absorption is likely to exist, and this may for example influence outcomes and cause variability in the duration of time needed to optimise therapy. In addition, the use of manipulated dosage forms can lead to inaccurate dosing. It is likely that many paediatric patients across Europe are exposed to this potential variability (**Appendix L**). This may also have an impact on the interpretation of published ACE-I efficacy and safety data, where information on the drug formulation and its administration is often not reported. The panel judgement supports the idea that the marketing of age-appropriate formulations would be beneficial.

The results also show specific therapeutic attitudes upon which consensus was achieved. These statements might trigger the sharing of data that are being recorded on a routine basis in clinical practice to evaluate the outcomes of agreed treatment strategies, which may help confirm their effectiveness and/or define best candidates for therapy. It has been recognised that large observational studies, databases and registries, when well designed, could represent an alternative means by which to generate the much-needed clinical evidence (Gibbons et al., 2009; Rossano and Shaddy, 2014b). The agreement on the veracity of these statements might also contribute to the efficient dissemination of relevant paediatric research to the physicians for whom this information is important, which has been found to be an area that needs to be improved (Francke et al., 2008; Zak et al., 2017). Three of these statements considered the role of ACE-I in the context of CHD. In their judgement, the panel discouraged routine use in patients with pressure overloading lesions (statement 8) and single ventricle physiology (statement 9). Even though the results of the previous survey suggest that the prescribing of ACE-I in single ventricle patients is still extensive (**Appendix L**), the authors of the Infant Single Ventricle Trial (Hsu et al., 2010), the only large paediatric randomised controlled trial on ACE-I that has been published, concluded their results did not support the routine use of enalapril in this scenario. The ISHLT guideline recommendation in this regard (Kirk et al., 2014), which was undertaken as statement 9 for discussion, supports this conclusion. In contrast, the panel agreed in the second round of questions that children with valve regurgitation that are asymptomatic may benefit from ACE-I therapy (statement 7). Evidence indicates that adult patients with mitral and aortic regurgitation are good candidates for ACE-I only if symptoms and/or left ventricular dysfunction exist, and it seems that practice among European paediatricians is largely influenced by this (**Appendix L**). Data indicating benefit in paediatrics come from a small randomized controlled trial (Mori et al., 2000) and several observational studies (Alehan and Ozkutlu, 1998; Calabrò et al., 1999), all of which included only asymptomatic patients. This evidence is

limited, but collaboration may contribute to the elucidation of patient subgroups whom would especially benefit.

The panel also agreed on the two statements regarding the use of beta-blockers in DCM-related heart failure. Consensus existed that beta-blockers should be considered in the therapy of asymptomatic children, and that they should be used in combination with an ACE-I (statements 10 and 11). In adults, a combination of beta-blocker with an ACE-I has proven benefit in asymptomatic patients with left ventricular dysfunction that have a history of myocardial infarction, although advantages when this is not the case are less clear and recommendations are not uniform (Yancy et al., 2013; Ponikowski et al., 2016). Paediatric data in this scenario are scarce (Alabed et al., 2016), and a marked division of opinion seems to exist among European paediatricians in this regard (Appendix K), however the expert panel judgement supports the potential benefits of this practice.

The 3 non-consensus statements identified in this Delphi study may provide greater visibility of some aspects of clinical practice which have a high degree of disparity of opinions among physicians. Two of these are directly related to aspects of heart failure treatment that have great potential to influence the long-term benefits of therapy. The first relates to optimal ACE-I maintenance dose in paediatrics (statement 5). Some of the experts in the panel agreed that a target dose should be aimed for, while others considered up-titration should be stopped once improvement is observed. This marked division of opinion is consistent with the results of the previous survey (**Appendix L**). Evidence in adults indicates that the efficacy of ACE-I in heart failure patients with left ventricular dysfunction in terms of mortality and hospitalizations reduction is closely related to dose level and that these effects are explained by mechanisms that probably do not play an important role in the control of symptoms (López-Sendón et al., 2004). Thus a response-based maintenance dose selection does not seem to be appropriate and aiming towards the target doses used in pivotal clinical trials, or failing this, towards the highest tolerated dose,

is recommended in adults (Ponikowski et al., 2016). On the other hand, unlike in adults, in paediatrics the origin of heart failure is very often multifactorial and not limited to ventricular dysfunction (Hsu and Pearson, 2009). No dose-effectiveness studies in paediatrics have established the existence of a target dose that produces benefits analogous to those that have been observed in adults and difficulties in achieving high ACE-I doses in the paediatric population have been reported (Hsu et al., 2010). Clinicians may consider comparing outcomes in groups of patients treated according different strategies, which may help establish a common criterion to treat paediatric patients in the most effective way. The same approach would apply to the topic addressed in the second of these non-consensus statements, which relates to the timing of introduction of aldosterone antagonists (statement 12). Results of the previous survey (**Appendix L**) revealed that aldosterone antagonists are frequently prescribed to children as part of the initial therapy of symptomatic heart failure, perhaps for their potassium sparing diuretic. However, evidence in adults supports the use of low-dose aldosterone antagonists as add-on therapy in patients that remain symptomatic despite initial therapy to improve prognosis (Ponikowski et al., 2016). Data in paediatrics in this regard are lacking. Some subgroups of paediatric patients have a marked poor prognosis, with a 5-year risk of death or cardiac transplantation of around 50% (Towbin et al., 2006). It would therefore be prudent to maximise available expert knowledge to drive decisions regarding those treatment strategies.

3.4.1 Validity and limitations

The results of a Delphi process are based on a synthesis of the opinions of a group, meaning that from question to question, some of the individual experts would differ with the consensus view. Furthermore, "the existence of a consensus does not mean that the correct answer has been found" (Hasson et al., 2000). A Delphi process is not intended to provide definitive answers but is rather a means of maximising the benefits from having informed panels consider a problem (Jones and Hunter, 1995).

No universally agreed guidelines on the use of the Delphi technique exist, but a thorough procedure for the design of the study has been followed and all relevant methodological aspects have been reported with transparency. Characteristics of the expert panel members (paediatricians dedicated to cardiology, 92% working in hospital paediatric cardiology units and with more than 10 years of experience in the field with representation of all four regions of Europe) and the lack of dropouts in the second study round are positive indicators of the quality of this study (Hsu and Sandford, 2007). Even though it cannot be assured that a different group of physicians with expertise in paediatric cardiology would have produced the same results, findings from Duffield (1993) and Akins *et al.* (2005) "indicate that the response characteristics of a small expert panel in a well-defined knowledge area are stable in light of augmented sampling."

This study has the limitations inherent to the Delphi technique (Hasson et al., 2000). It is also recognised that the study is limited by the simplified manner in which the statements presented for debate addressed topics of great complexity. An exhaustive questionnaire would have required considerable demands of time and effort to the participants, which would have compromised the feasibility of the study. The study participants were selected from different backgrounds to assure that no interest or preconceived opinion was likely to dominate. However, it should be noted that one of the participants was directly involved in a study whose results were very relevant to the discussion regarding the pertinence of angiotensin-converting-enzyme-inhibitors in single ventricle patients, and his opinion on that statement was not unexpected. Nevertheless, a different response by this participant would not have changed the global consensus results on that particular statement. Furthermore, one of the expert panel members was researcher in the LENA project, and had been involved in previous discussions on study-relevant topics.

3.4.2 Conclusions

This Delphi process reflects the opinion of a 13-member expert panel of paediatricians experienced in cardiology. Consensus was achieved on 11 out of the 14 statements addressing controversial aspects of paediatric heart failure therapy presented for discussion. Agreement existed on the importance of a set of topics relevant to the standardization of therapy: developing guidance on the approach towards adverse events in the context of ACE-I therapy, promoting the correlation of paediatric validated scores with therapeutic recommendations in further guidelines and reducing heterogeneity associated with unlicensed ACE-I formulations. Agreement was also achieved on discouraging routine use of ACE-Is in single ventricle physiology and pressure overloading lesions, whereas the panel agreed that children with mitral or aortal regurgitation that are asymptomatic might benefit from therapy and that beta-blockers may be recommended for asymptomatic DCM patients. The marked division of opinion regarding the criterion according to which the optimal ACE-I maintenance dose should be established, and the role of aldosterone antagonists are remarkable, since the attitudes discussed in both statements have potential to influence the long-term benefits of therapy.

When evidence is scarce and contradictory, the insights of experts provide a valuable contribution to the decision-making process (Jones and Hunter, 1995; Fick et al., 2003; Gurvitz et al., 2013). The output from consensus approaches is rarely an end in itself, dissemination and further use of findings is the ultimate aim of such activities (Jones and Hunter, 1995). The results of this study might contribute to disseminate paediatric evidence available and serve to promote reducing unjustified variability in everyday practice. Areas of common thinking and motivation have been found, which can provide a means of triggering scientific collaboration to cover the named areas of need, both in the form of data sharing to evaluate therapy outcomes and in developing consensus documents that approach specific topics in depth. Until therapeutic recommendations can be made on the basis of solid evidence

derived from paediatric randomized controlled trials, this work advocates making the best use of available knowledge. This work will hopefully help raise awareness that, though not optimal, other research methods can contribute to advancing the goal of safe and effective heart failure pharmacotherapy in children.

X. Final summary of the thesis and overall conclusions

This thesis has provided an overview of drug prescribing patterns for paediatric heart failure management across Europe and the criteria applied when using ACE-I to treat this condition. The information obtained has enabled to gain insight into real practice issues of the pharmacotherapy for this population. The subsequent structured discussion means a Delphi process has enabled to record the judgement of an international group of paediatricians dedicated to cardiology on controversial aspects of heart failure pharmacotherapy and maximise the benefits from having an informed panel consider these problems.

In the first part of the thesis (**Chapters 1** and **2**), a Europe-wide survey study on the pharmacological management of paediatric heart failure was conducted among physicians dedicated to paediatric cardiology. Hundred physicians representing 100 different hospitals in 27 European countries participated. Results presented in **Chapter 1** show that pharmacological therapy appears to have become an integral part of paediatric heart failure management across Europe and that this seems to be characterised by a lack of uniformity. Twenty-five different drug therapy combinations were reported for the initial therapy of DCM-related symptomatic heart failure. Prescribing practices consistent with adults' evidence were observed and also marked deviations, namely the frequent use of aldosterone antagonists as initial therapy. Drug use in asymptomatic patients appears to be widespread, and a large proportion of physicians select a drug regimen not even supported by adult data (different from ACE-I monotherapy or ACE-I-beta-blocker two-drug only combination). This seems to be a particularly relevant topic to be prioritised in future research since pharmacotherapy may have the potential of delaying or preventing the worsening of heart failure in these children. ACE-I seem key in paediatric heart failure treatment strategies both when DCM and CHD are the underlying causes. The survey results indicate that use of ACE-I in single ventricle patients seems frequent across Europe, in apparent

contradiction with current paediatric evidence (Hsu et al., 2010). This finding illustrates the challenge that changing from experiential practice to evidence-based medicine represents in paediatric cardiology (Li et al., 2011). Overall survey observations suggest, despite the marked differences in underlying pathophysiology, reliance on evidence in adults has a strong influence regarding decisions on ACE-I use in children with CHD.

The results presented in **Chapter 2** suggest that some reluctance to use ACE-I in newborns seems to exist, most probably due to safety concerns. Since an early therapy introduction may have a positive impact in the disease prognose (Lewis and Chabot, 1993; Kantor et al., 2010), this finding highlights the need for guidance to allow an optimal use of ACE-I in the youngest population. Disparate ACE-I dosing criteria, potential formulation-induced variability and heterogeneity affecting therapy outcomes definition, suggest significant differences may exist in the risk-benefit profile children are exposed to. These observations clearly show that the collation and evaluation of systematic data to elucidate optimal ACE-I usage criteria in paediatrics should be a priority. Meanwhile, utilisation of best knowledge available should be maximised to seek agreement and reduce unjustified variability.

In the second part of the thesis (**Chapter 3**) a Delphi study was conducted among an international group of 13 paediatricians with expertise in cardiology. Controversial aspects of heart failure pharmacotherapy, that had been predominantly identified in the previous survey, were discussed in a two-round modified Delphi process. Fourteen statements were presented for discussion grouped under three categories; ACE-Is: Considerations for optimal dosage; ACE-Is for the management of CHD; Neurohumoral antagonists for the management of DCM-related heart failure. Agreement on the acceptance/rejection of 11 statements was achieved. Results show agreement on the importance of a set of topics relevant to the standardisation of the therapy as well as consensus upon specific therapeutic attitudes. When evidence is scarce and contradictory, the insights of experts can represent a valuable

contribution to the decision-making process (Jones and Hunter, 1995; Fick et al., 2003; Gurvitz et al., 2013). Rather than producing any changes in clinical practice, the results can be seen as a guide for further research steps, and a set of topics upon which scientific projects are more likely to be successfully implemented. Areas of common thinking and motivation have been found, which can provide a means of triggering scientific collaboration. The results might also contribute to disseminate available paediatric evidence and promote reducing unjustified variability in everyday practice. Furthermore, statements upon which a marked division of opinion existed might serve to give the topics discussed a greater visibility.

Interest in paediatric heart failure drug therapy has grown especially as a means by which to maintain cardiac and end-organ function until heart transplant or surgery can be performed, and/or to delay or avoid the need (Rossano and Shaddy, 2014a). The low incidence of paediatric heart failure, and the heterogeneity in underlying conditions and clinical presentation in the different paediatric ages, make it particularly difficult to conduct well-design randomised controlled trials in this population. Therefore, it is essential to consider alternative approaches to optimise pharmacotherapy in this population. Physicians dedicated to paediatric cardiology are evaluating outcomes and recording data on a routine basis that could contribute to generate the much-needed paediatric evidence. The existing heterogeneity in everyday practice difficults the comparability of data across centres as well as the interpretation of published research. In this thesis, possible starting points to working towards harmonisation in paediatric heart failure pharmacotherapy have been identified. The results might also serve to motivate data sharing to evaluate therapy outcomes. Furthermore, it has been shown that taking into consideration established prescribing practices may be relevant to plan successful studies. The findings of this thesis might provide a basis to design future research strategies and policies that help advance the goal of a safe and effective drug therapy in heart failure children.

XI. References

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XII. Appendices

Appendix A: Survey study - Reliability and validity testing of the survey instrument

A.1 Table of Contents

A.2 Reliability and validity testing: Introduction

Assessing questionnaires' reliability and validity has been recommended as part of survey research design best practice (Burns et al., 2008; Andres, 2012), however, no standards have been established on how these should be best evaluated or how to judge the acceptable levels. During the study and survey instrument design phase, discussions with experts, peer-review, pre- and pilot-testing served as a means by which repeatedly evaluate the questionnaire, identify weaknesses and offer and implement solutions (Andres, 2012). With the intention of further providing objective data to support the adequacy of the questionnaire in this regard, two formal tests were conducted. The reliability testing aimed at evaluating whether the questions had been designed in a clear and unambiguous way. The validity testing, aimed at assessing how well the questionnaire addressed the topic of interest and the study objective, and if the questions sought the information they intended to (content and face validity) (Burns et al., 2008; Andres, 2012).

A.3 Reliability testing: methods, results and discussion

A.3.1 Reliability testing: methods

A test-retest strategy was chosen to assess the degree of reliability of the questionnaire (Burns et al., 2008). With this method, it is evaluated whether consistent results are obtained when the same questions are asked to the same individuals at different times. The answers of the expert panel members with specialised knowledge in paediatric cardiology who completed the questionnaire pre-final version as part of the pilot-testing (October 2014) and later on the questionnaire final version as survey study participants (January - May 2015) were analysed. Responses recorded were used as "test" and "retest" respectively. **Figure A1** provides an overview of the procedure followed for the processing and evaluation of data during the reliability testing.

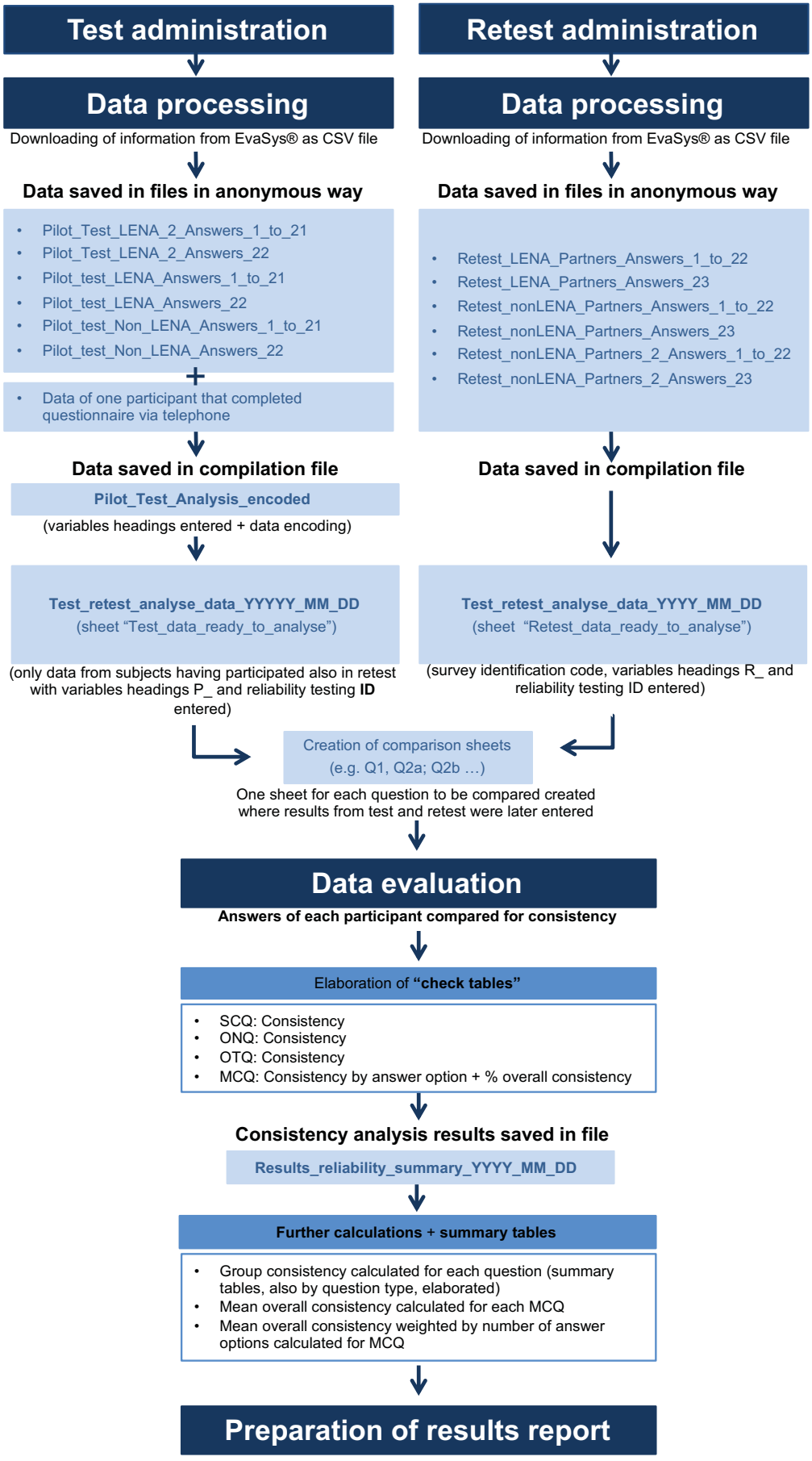


Figure A1. Overview of the procedure followed for data processing and evaluation during reliability testing

Since as a result of the pilot-testing some modifications in questionnaire were introduced, questionnaire final and pre-final version differed slightly. This was adequately taken into consideration for the analysis. Question numbering used for the presentation of results corresponds to that from questionnaire final version (**Appendix B**). Question 3 displayed up to four times, one for each of the age groups that had been selected in question 2. The following nomenclature was used to differentiate them: 3a, newborns; 3b infants and toddlers; 3c, children; 3d, adolescents. Where a question included sub-questions, these were also differentiated for evaluation: e.g. question 8.1 and 8.2. Open text fields that displayed when an "other" option was selected or further comments on a topic were requested were not considered for analysis.

Consistency of the individual responses provided by each participant was defined and evaluated for each question type as follows:

- Single choice question (SCQ): participant selected an identical answer option in test and retest.
- Open question (OQ):
    - Open text question (OTQ): participant entered an identical/equivalent answer in test and retest.
    - Open numeric question (ONQ): participant entered an identical figure in test and retest, or where a range was entered (either in test, retest or both) the answers provided overlapped.
- Multiple choice question (MCQ): participant selected and unselected identical answer options in test and retest. Since questions with 4 to 8 answer options existed, comparability with consistency results for SCQ and OQ was limited. To better describe how similar or different the answers provided by participants had been also the concept "overall

consistency" (OC), the percentage of identical answer options selected by the participant in test and retest, was defined.

Where a question did not apply to a participant, this was marked as NA (not applicable). Where data were not comparable for reliability testing (e.g. answers of a participant led to different questions to display in test and retest), this was marked as CNP (comparison not possible). Illustrative examples of how the test-retest comparison was performed for each question type are provided in **Tables A1**, **A2** and **A3**.

Table A1. Example of test-retest evaluation of a single choice question. Question 3.1.b: Which ACE-I do you consider as your first choice for infants and toddlers (28 days - 23 months)?

ID	Test	Retest	Consistency
1	Captopril	Captopril	**Yes**
2	Captopril	Captopril	**Yes**
3	Captopril	Captopril	**Yes**
4	NA	Captopril	**CNP**
5	Captopril	Captopril	**Yes**
6	Captopril	Captopril	**Yes**

Participant 4 reported in "test" not prescribing ACE-I to infants and toddlers. Thus, this question did not display for him in test and consistency of answers could not be evaluated for him. The inconsistency that led to this, was adequately evaluated in the corresponding question. All 5 participants whose consistency for this question could be evaluated gave a consistent answer, thus group consistency here was 100%. ID, participant identification number; CNP, comparison not possible

Table A2. Example of test-retest evaluation of an open question. Question 3.2.d: Starting dose in mg/kg per dose of first choice ACE-I in adolescents (12 - 18 years)

ID	Test	Retest	Consistency
1	0,1	NA	**CNP**
2	0,025-0,05	0,05	**Yes**
3	0,1	0,1	**Yes**
4	0,05	0,03	**CNP**
5	0,1	0,1	**Yes**
6	0,05	0,01	**No**

Participant 4 selected a different first-choice ACE-I for adolescents in test and retest. Participant 1 declared not using ACE-I in this age group in the retest. Consistency of these participants could not be evaluated for this question. The inconsistency that led to this, was adequately evaluated in the corresponding question. Three out of the 4 participants whose answers could be evaluated for consistency in this question, gave a consistent answer, thus group consistency 75%.ID, participant identification number; CNP, comparison not possible

Table A3. Example of test-retest evaluation of a multiple-choice question. Question 1: Which cardiac diseases related to heart failure development do you manage with ACE-I?

	DCM			CHD			None			Other			
ID	Test	Retest	**C**	Test	Retest	**C**	Test	Retest	**C**	Test	Retest	**C**	**OC [n/total(%)]**
1	•	•	**Yes**	•	•	**Yes**	○	○	**Yes**	○	•	**No**	**3/4 (75)**
2	•	•	**Yes**	•	•	**Yes**	○	○	**Yes**	○	○	**Yes**	**4/4 (100)**
3	•	•	**Yes**	•	•	**Yes**	○	○	**Yes**	•	○	**No**	**3/4 (75**
4	•	•	**Yes**	○	•	**No**	○	○	**Yes**	○	○	**Yes**	**3/4 (75)**
5	•	•	**Yes**	•	•	**Yes**	○	○	**Yes**	○	○	**Yes**	**4/4 (100)**
6	•	•	**Yes**	○	○	**Yes**	○	○	**Yes**	○	○	**Yes**	**4/4 (100)**

Mean overall consistency for this question was 88% and group consistency 50%. •, answer option selected; ○, answer option not selected; C, consistency for each single answer option; CHD, congenital heart defect; DCM, dilated cardiomyopathy; ID, participant identification number; OC, overall consistency

For each question the group consistency was calculated, a concept that was defined as follows:

$$\text{Group consistency (\%)} = \frac{\text{Participants that gave a 100\% consistent answer}}{\text{Participants whose consistency could be evaluated for that question}} \times 100$$

When evaluating the group consistency in MCQ only participants for whom the calculated OC was 100% were accounted as consistent. Mean group consistency was further calculated for each question type (SCQ, OQ, MCQ) as follows:

$$\text{Mean group consistency (\%)} = \frac{\sum \text{Group consistency calculated for a certain question type}}{\text{Number of questions of that type}}$$

For each MCQ also the mean OC and then the global mean OC of all MCQ weighted by number of answer options was calculated:

$$\text{Mean OC (\%)} = \frac{\sum \text{OC of each participant in a MCQ}}{\text{Participants whose consistency could be evaluated for that MCQ}} \times 100$$

$$\text{Global mean OC weighted by number of answer options (\%)} = \frac{\sum(\text{Mean OC} \times \text{Number of answer options of that MCQ})}{\sum \text{Answer options of all MCQ}}$$

A.3.2 Reliability testing: results

The answers of six of the expert panel members with specialised knowledge in paediatric cardiology from 3 countries (The Netherlands, Serbia and Germany) were analysed. Responses to 44 questions (considering sub-questions) were evaluated; 22 SCQ, 10 OQ and 12 MCQ.

For SCQ, the calculated mean group consistency was 76% (range 33 to 100%). In 6 of the 22 questions (27%) all participants gave a consistent answer (100% group consistency). For 14 questions the group consistency was ≥75%. Detailed results are displayed in **Figure A2**.

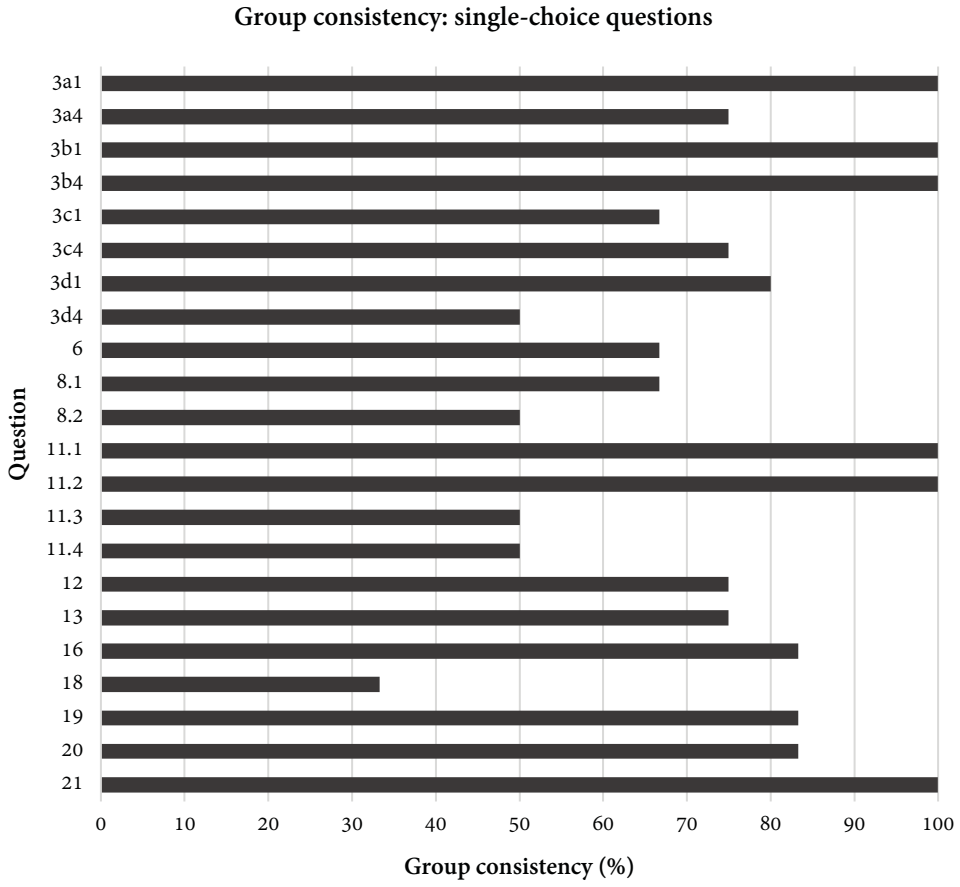


Figure A2. Group consistency: single choice questions. In question 18 ("According to your experience, how would you grade the impact of pharmacological therapy on the course of the disease in your paediatric heart failure patients?"), the punctuation selected by 3 out of the 4 participants that did not replicate the answer in retest, differed only in one point. In question 19 ("Would you like to add any comment that you consider relevant to this survey?"), the inconsistency can be largely attributed to the disposition of participants in that exact moment to make further comments. In question 20 ("How many years of experience do you have caring for children with heart failure?") the difference in the responses given in test (">5 to 10 years") and retest (">10 years") by one participant, is attributable to the period of time that elapsed.

For OQ (open numeric and open text questions), the calculated mean group consistency was 67% (range 25 to 100%). In 2 out of 10 questions, all experts gave a consistent answer (100% group consistency). Results are shown in **Figure A3**.

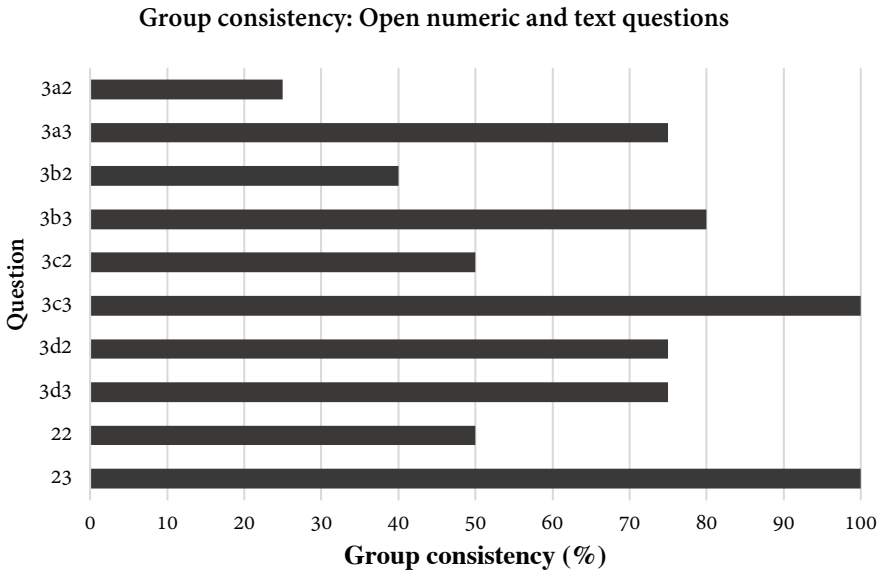


Figure A3. Group consistency: Open numeric and text questions

With regard to MCQ, the group consistency ranged from 0% to 67%. Participants' individual overall consistency ranged from 50 to 100%. The mean overall consistency calculated for each of the 12 MCQ ranged from 68 to 92% and the global mean overall consistency weighted by number of answer options was of 84%. Results are shown in **Table A4**.

Table A4. Test-retest analysis results - multiple-choice questions

		Multiple-choice question												
		1	**2a**	**2b**	**3a5**	**3b5**	**3c5**	**3d5**	**4**	**5**	**7**	**14**	**15**	**17**
Participant ID		**Overall consistency (OC)**												
		n/total* (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)
1		3/4 (75)	NA	3/4 (75)	6/7 (86)	6/7 (86)	6/7 (86)	CNP	3/4(75)	3/4(75)	6/8 (75)	8/8 (100)	7/8 (88)	8/8 (100)
2		4/4 (100)	NA	4/4 (100)	5/7 (71)	6/7 (86)	5/7 (71)	6/7 (86)	4/4 (100)	4/4 (100)	6/8 (75)	8/8 (100)	7/8 (88)	7/8 (88)
3		3/4 (75)	NA	4/4 (100)	NA	7/7 (100)	5/7 (71)	6/7 (86)	4/4 (100)	3/4 (75)	5/8 (63)	8/8 (100)	7/8 (88)	NA
4		3/4 (75)	NA	3/4 (75)	NA	CNP	NA	CNP	3/4 (75)	3/4 (75)	6/8 (75)	7/8 (88)	7/8 (88)	7/8 (88)
5		4/4 (100)	NA	4/4 (100)	7/7 (100)	7/7 (100)	NA	4/7 (57)	2/4 (50)	4/4 (100)	5/8 (63)	6/8 (75)	8/8 (100)	6/8 (75)
6		4/4 (100)	NA	4/4 (100)	5/7 (71)	5/7 (71)	5/7 (71)	3/7 (43)	4/4 (100)	4/4 (100)	6/8 (75)	7/8 (88)	7/8 (88)	8/8 (100)
	Mean OC (%)	(88)	NA	(92)	(82)	(89)	(75)	(68)	(83)	(88)	(71)	(92)	(90)	(90)
	Group consistency	n/total** (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)
		3/6 (50)	NA	4/6(67)	1/4 (25)	2/5 (40)	0/4 (0)	0/4 (0)	3/6 (50)	3/6 (50)	0/6 (0)	3/6 (50)	1/6(17)	2/5 (40)

* n: number of consistent answer options selected in test and re-test; total: number of answer options in that particular question

** n: number of participants that gave a 100% consistent answer; total: participants whose consistency was evaluated in that particular question

CNP, comparison not possible; ID, identification number; NA, not applicable; OC, overall consistency

In **Table A5** summary of group consistency evaluation by question type is shown. A global summary of group consistency evaluation is provided in **Table A6**. For 34 out of the 44 questions analysed (77%), the calculated group consistency was ≥50%. In 8 questions all participants gave a consistent answer (group consistency 100%). In 3 of the questions the calculated group consistency was 0%, however these were all MCQ for which the calculated overall consistency ranged from 43 to 86%.

Table A5. Summary of group consistency evaluation by question type

	Group consistency				
	0%	**<50%**	**≥50 %**	**≥75%**	**100%**
Question type	n/total (%)	n/total (%)	n/total (%)	n/total (%)	n/total (%)
SCQ	0/22 (0)	1/22 (5)	21/22 (95)	14/22 (64)	6/22 (27)
MCQ	3/12 (25)	7/12 (58)	5/12 (42)	0/12 (0)	0/12 (0)
OQ	0/10 (0)	2/10 (20)	8/10 (80)	6/10 (60)	2/10 (20)

MCQ, multiple-choice question; OQ, open question; SCQ, single-choice question

Table A6. Summary of group consistency evaluation (all question types)

Group consistency	**Number of questions**	
	n/total	(%)
0-24%	4/44	9
25-49%	6/44	14
50-74%	14/44	32
75-100%	20/44	45

A.3.3 Reliability testing: Discussion

The calculated group consistency for the SCQ (mean 76% and group consistency ≥75% for 64% of the questions) and OQ (mean 67% and group consistency ≥75% for 60% of the questions) seemed to be similarly high. Global mean overall consistency weighted by number of answer options for the 12 MCQ assessed was 83%, which also indicates a high degree of reproduction of responses.

Even though, no formal cut-off values or criteria exist to judge the acceptable level of reliability of questionnaires within the scientific community, Andres (2012) states that "exact replication of the results of a survey research project is highly unlikely. But if similar trends in the findings can be

determined, the measures and methods employed can be considered to be reliable." Even though the sample size was insufficient for any statistical analysis to be applied, the results described reflect a high degree of stability of responses.

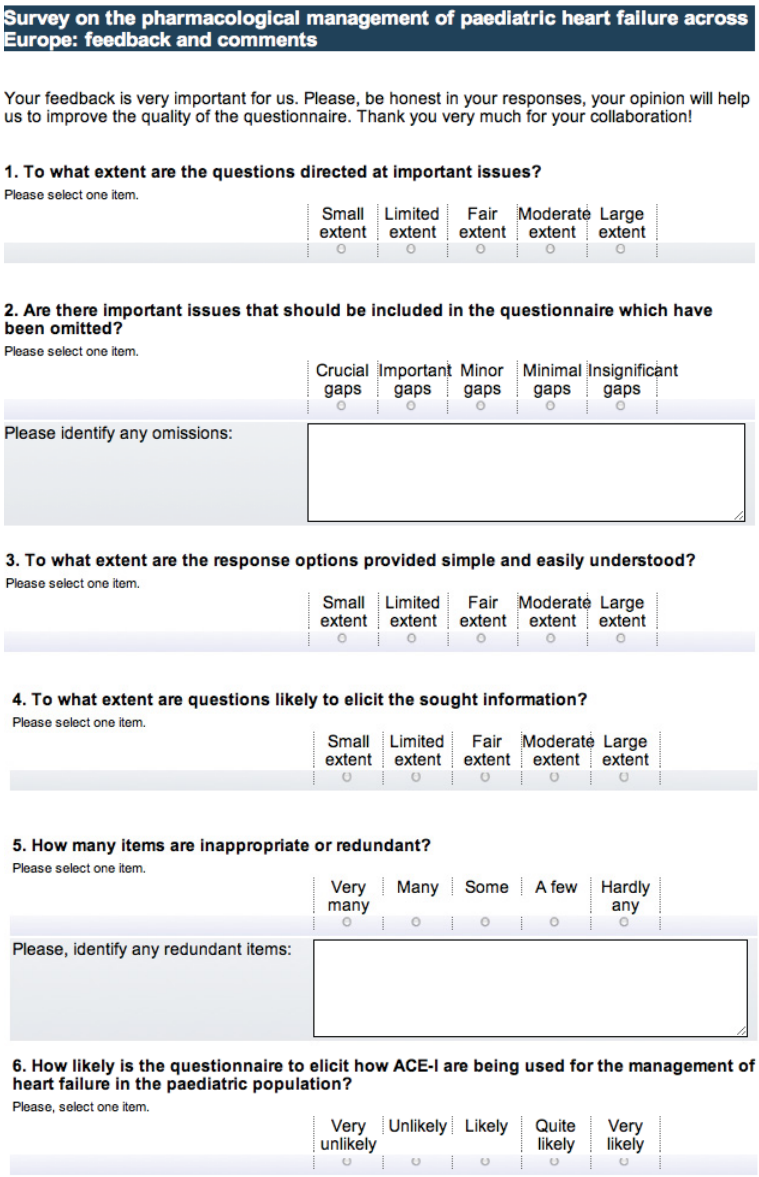
The nature of the topic addressed needs to be taken into consideration to put the reliability testing results into perspective. Different answers at different times do not necessary reflect a lack of consistency motivated but unclear questions. Real changes in the therapeutic strategies or clinicians' opinions might well exist. Since little solid evidence regarding the pharmacological management of paediatric heart failure exists, medical practice is subject to constant change. New publications and experiences in daily practice, as well as the increased awareness to the subject triggered by the survey pre-test itself, might be responsible for some of the differences observed between test and retest responses. Furthermore, aiming at maintaining the motivation and commitment of the expert panel (some of the experts were expected to be later participants of the final survey and their input in later stages of the research was highly desirable) the decision was made to avoid an extra round of questioning by using the pilot-test as test and the responses provided to the questionnaire final version during the conduction of the survey study as retest. Thus, instead of the usual 2-3 weeks (Burns et al., 2008), a period of about 8 months elapsed between the administration of the two questionnaires, which can also have impacted the reliability results in a negative way.

The findings presented here are complementary to the evaluation of reliability-relevant aspects investigated through peer-reviews and input from the expert panel during the survey instrument development procedure and seem to confirm that no relevant ambiguities or unclarities existed in the questionnaire.

A.4 Validity testing: methods, results and discussion

A.4.1 Validity testing: methods

A series of seven questions addressing the survey instrument content and face validity was passed to participants in October 2014 after pilot-testing. This was an adaptation of one proposed by Burns et al. (2008) (**Figure A4**). For practical reasons, an eighth question regarding questionnaire completion time was included, but not analysed as part of the validity testing.



Survey on the pharmacological management of paediatric heart failure across Europe: feedback and comments

Your feedback is very important for us. Please, be honest in your responses, your opinion will help us to improve the quality of the questionnaire. Thank you very much for your collaboration!

1. To what extent are the questions directed at important issues?

Please select one item.

Small extent	Limited extent	Fair extent	Moderate extent	Large extent
○	○	○	○	○

2. Are there important issues that should be included in the questionnaire which have been omitted?

Please select one item.

Crucial gaps	Important gaps	Minor gaps	Minimal gaps	Insignificant gaps
○	○	○	○	○

Please identify any omissions:

3. To what extent are the response options provided simple and easily understood?

Please select one item.

Small extent	Limited extent	Fair extent	Moderate extent	Large extent
○	○	○	○	○

4. To what extent are questions likely to elicit the sought information?

Please select one item.

Small extent	Limited extent	Fair extent	Moderate extent	Large extent
○	○	○	○	○

5. How many items are inappropriate or redundant?

Please select one item.

Very many	Many	Some	A few	Hardly any
○	○	○	○	○

Please, identify any redundant items:

6. How likely is the questionnaire to elicit how ACE-I are being used for the management of heart failure in the paediatric population?

Please, select one item.

Very unlikely	Unlikely	Likely	Quite likely	Very likely
○	○	○	○	○

Figure A4. Questionnaire on survey questionnaire validity (continued in next page)

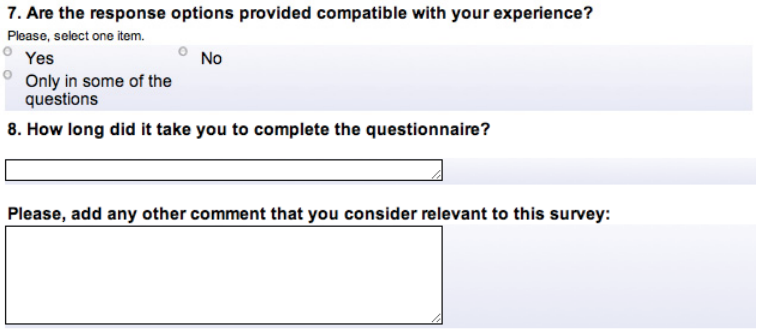


Figure A4. (continued) Questionnaire on survey questionnaire validity

Figure A5 provides an overview of the data processing and evaluation procedure during validity testing. For each question, descriptive statistics (absolute and relative frequency of the answers options selected) was calculated. Comments given on the questionnaire were listed.

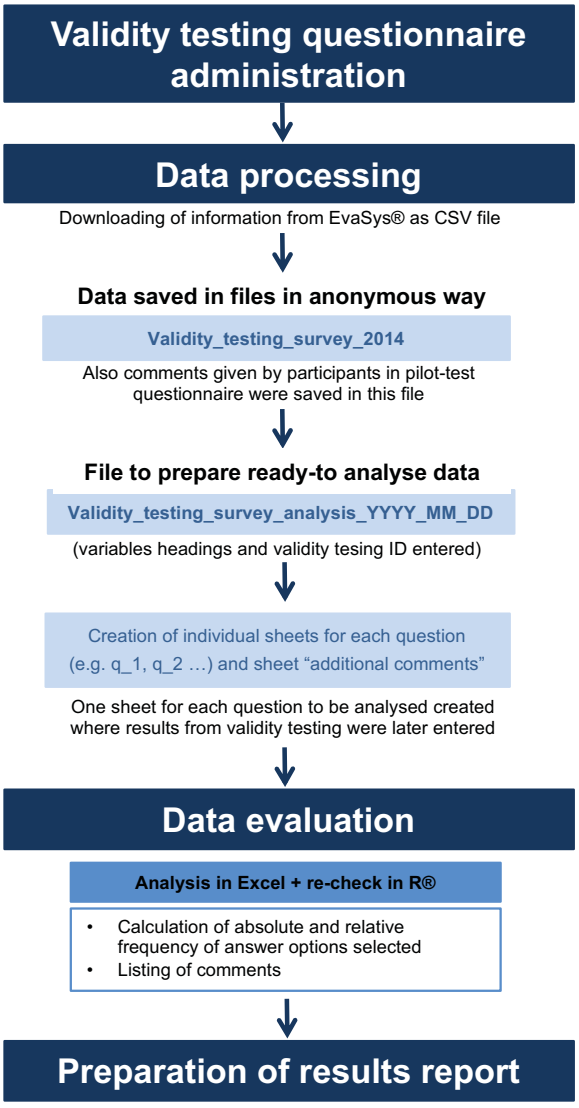


Figure A5. Overview of the data processing and evaluation procedure during validity testing.

A.4.2 Validity testing: results

Four members of the expert panel agreed in answering the questionnaire. Results are presented in **Table A7**.

Table A7. Validity testing results

	Questions	Response options	n/total	(%)
1.	**To what extent are the questions directed at important issues? ***	Small extent	0/4	0
		Limited extent	0/4	0
		Fair extent	0/4	0
		Moderate extent	1/4	25
		Large extent	2/4	50
2.	**Are there important issues that should be included in the questionnaire which have been omitted?****	Crucial gaps	0/4	0
		Important gaps	0/4	0
		Minor gaps	1/4	25
		Minimal gaps	2/4	50
		Insignificant gaps	1/4	25
3.	**To what extent are the response options provided simple and easily understood?**	Small extent	0/4	0
		Limited extent	0/4	0
		Fair extent	0/4	0
		Moderate extent	1/4	25
		Large extent	3/4	75
4.	**To what extent are questions likely to elicit the sought information?**	Small extent	0/4	0
		Limited extent	0/4	0
		Fair extent	0/4	0
		Moderate extent	1/4	25
		Large extent	3/4	75
5.	**How many items are inappropriate or redundant?**	Very many	0/4	0
		Many	0/4	0
		Some	0/4	0
		A few	0/4	0
		Hardly any	4/4	100
6.	**How likely is the questionnaire to elicit how ACE-I are being used for the management of heart failure in the paediatric population?**	Very unlikely	0/4	0
		Unlikely	0/4	0
		Likely	1/4	25
		Quite likely	2/4	50
		Very likely	1/4	25

(continued)

Table A7. (continued) Validity testing results

	Questions	Response options	n/total	(%)
7.	**Are the response options provided compatible with your experience?**	Yes	3/4	75
		No	1/4	25
		Only in some questions	0/4	0

*One participant did not answer question 1.

** One participant identified the following gaps: *"Importance of Licencing by EMA. - Sequence of drug therapy (not only primary and secondary, but also next steps: for example, In which order do you start heart failure treatment (give a number to each drug group; if you enter two drugs simultaneously, give them the same number): 1 loop diuretics 1 thiazide diuretics 1 spironolactone 2 beta-blocker 2 ACE-I ARB 3 digoxin anticoagulation"*. Additional comments provided by participants were the following: *"You might have a look to the cardiomyopathy registry of the Deutsches Kompetenznetz für Angeborene Herzfehler"; "For the DCM questions are fairly straightforward. For cong heart disease options are presented as all or nothing options, which is often not the case" "Regarding q9 stop increasing/withdrawing ACE-I not only depends on a % drop in RR, but also on absolute level and other parameters like kidney function. Regarding q10 we treat with ACE-I if pressure overload is secondary to hypertension. Regarding q 17: as alluded to previously, we simply don't know for sure to what extent and in whom HF meds are efficacious in kids, some (many?) may recover irrespective of meds, while other die or get transplanted despite optimal therapy".*

A.4.3 Validity testing: discussion

The results of the validity questionnaire seem unambiguously positive. Only one out of the four participants gave a negative answer to one of the questions ("Are the response options provided compatible with your experience?"). However, his remaining judgements were positive and when asked "To what extent are the questions likely to elicit the sought information?" he selected the maximal punctuation, "Large extent".

Based on these findings, and together with the input received from the expert panel throughout the questionnaire development, it can be concluded that no major topics were omitted, that the questionnaire measured what it intended to measure and that it successfully addressed the study objective.

A.5 Reliability and validity testing: final conclusions

Validity and reliability of the survey instrument are key features impacting the quality of a survey study. These aspects have been in focus throughout the study design and questionnaire development phase. Recommendations for survey and questionnaires design best practice have been followed and

discussions with experts, peer-review, pre- and pilot-testing served as a means by which repeatedly evaluate the questionnaire, identify weaknesses and offer and implement solutions (Andres, 2012). Even though no firm conclusions can be drawn from these two tests, it is considered that the results can be described as satisfactory and support the quality of the questionnaire.

Appendix B: Survey study – Questionnaire[1]

European survey on the pharmacological management of paediatric heart failure

Welcome to the European survey on the pharmacological management of paediatric heart failure

Thank you for agreeing to participate in this survey. Your responses will provide very valuable information.

The questionnaire will not take you more than 15 minutes. Please, read the instructions for each question carefully. There are multiple choice, single choice and open questions in which you are required to write an answer. The buttons "previous" and "next" at the bottom of the page will allow you to move from one question to another.

Please, try to answer the questionnaire in one session, otherwise your answers will not be sent correctly. If you left the questionnaire open for more than 10 minutes without working on it, you would need to close it and restart it by using your link again. If you have any difficulty or questions, do not hesitate to contact us at cristina.castro.diez@uni-duesseldorf.de

Angiotensin-converting enzyme inhibitors (ACE-I) use for the management of paediatric heart failure

1. Which cardiac diseases related to heart failure development do you manage with ACE-I?
Please select all items that apply to you.

- ☐ Dilated cardiomyopathy
- ☐ Congenital heart defects
- ☐ None
- ☐ Other (please specify in the box below)

2. Which paediatric age groups do you treat with ACE-I?
Please select all items that apply to you.

- ☐ Newborns (0-27 days)
- ☐ Infants and toddlers (28 days-23 months)
- ☐ Children (2-11 years)
- ☐ Adolescents (12-18 years)

[1] Please note that the questionnaire was not presented to participants in the present format but using the web-survey platform EvaSys®.

ACE-I choice and dosage by age group for the management of paediatric heart failure

The following question is the longest of the questionnaire, but the information you will provide is essential for a better understanding of the way ACE-I are being used in paediatrics. It will not take you more than 5 minutes. Thank you again for your time!

3. Which ACE-I do you consider as your first choice for NEWBORNS (0-27 DAYS)?

ACE-I
Please select one item from the list.

☐Benazepril	☐Fosinopril	☐Quinapril
☐Captopril	☐Imidapril	☐Ramirpil
☐Cilazapril	☐Lisinopril	☐Trandolapril
☐Enalapril	☐Moexipril	☐Zofenopril
☐Espirapril	☐Perindopril	☐Other (please specify in the box below)

Starting dose in mg/kg per DOSE
Please type the dose in the box.

Target / Maintenance dose in mg/kg per DAY
Please type the dose in the box.

In how many doses is the target / maintenance DAILY dose divided?
Please select one item from the list.

☐One single dose
☐Two divided doses
☐Three divided doses
☐Four divided doses

Why is this ACE-I your first choice for NEWBORNS?
Please select all items that apply to you.

☐More experience with use
☐Most appropriate formulation available
☐More convenient to parents/patients
☐Recommended in guidelines or books
☐Established in hospital protocols
☐No specific reason
☐Other (please specify in the box below)

4. Which ACE-I formulation do you prescribe when the adults formulation is not suitable for a patient?
Please select all items that apply to you.

- ☐ Formulation provided by my hospital pharmacy
- ☐ Formulation provided by community pharmacy
- ☐ Formulation prepared by parents at home using the adults formulation
- ☐ Other (please specify in the box below)

5. What kind of formulation is it?
Please select all items that apply to you.

- ☐ Liquid formulation
- ☐ Capsules
- ☐ Powder
- ☐ Other (please specify in the box below)

6. Do you increase the dose of ACE-I to your target although patient has already improved with a lower dose?
Please select one item.

- ☐ No
- ☐ Yes
- ☐ Sometimes (please specify in the box below)

Effectiveness and toxicity assessment of ACE-I in paediatric heart failure

7. How do you assess the effectiveness of ACE-I in your paediatric patients?
Please select all items that apply to you.

- ☐ Clinical judgement according to changes in signs and symptoms
- ☐ Needs of anticongestive medication
- ☐ Parents' opinion/ perception
- ☐ Clinical scores (e.g. Ross, NYHA)
- ☐ Echocardiographic or radiographic parameters
- ☐ Level of natriuretic peptide
- ☐ Quality of life scores
- ☐ Other (please specify in the box below)

We know, it is difficult to give a simple answer to the following question. Please, we would like you to select the option that most approximates to your practice.

8. If deterioration of the renal function is detected,

which serum creatinine increase relative to baseline value makes you stop increasing the dose of ACE-I?

Please select one item.

- ☐ 1.1 to 1.4 times
- ☐ 1.5 to 1.9 times
- ☐ 2.0 to 2.9 times
- ☐ 3 times or more
- ☐ No formal limit used

which serum creatinine increase relative to baseline value makes you withdraw the therapy with ACE-I?

Please select one item.

- ☐ 1.1 to 1.4 times
- ☐ 1.5 to 1.9 times
- ☐ 2.0 to 2.9 times
- ☐ 3 times or more
- ☐ No formal limit used

Please add any additional comment that you consider relevant to this question:

9. If hypotension is detected, do you follow pre-established formal blood pressure limits that make you

	Yes	No
stop increasing the dose of ACE-I? Please select one item.	☐	☐
withdraw the therapy with ACE-I? Please select one item.	☐	☐

10. What type of limit do you use?

Please select all items that apply to you.

- ☐ Percentage decrease relative to baseline value
- ☐ Absolute blood pressure values according to age
- ☐ Other (please specify in the box below)

ACE-I in paediatric patients with congenital heart diseases

11. Which of your paediatric patients with congenital heart diseases do you treat with ACE-I?
Please select one option for each congenital heart disease.

	Asymptomatic	Symptomatic	Both	None
Left-to-right shunt lesions	☐	☐	☐	☐
Pressure overloading lesions	☐	☐	☐	☐
Single ventricle lesions	☐	☐	☐	☐
Valve regurgitation	☐	☐	☐	☐

Please add any additional comment that you consider relevant to this question:

12. Do you use ACE-I for the management of any other congenital heart disease?
Please select one item.

☐No
☐Yes (please specify in the box below)

13. How long do you treat your patients with congenital heart diseases with ACE-I after heart surgery?
Please select one item.

☐< 1 month
☐1 to 3 months
☐> 3 months to 6 months
☐> 6 months
☐I do not use ACE-I in my patients after heart surgery

Pharmacologic management of paediatric heart failure in patients with dilated cardiomyopathy

14. When treating dilated cardiomyopathy, which drugs do you use as initial therapy of symptomatic patients, who are not dependent on intravenous inotropic/vasoactive drugs (e.g. dobutamine, milrinone, nitroglycerin, levosimendan...)?
Please select all items that apply to you.

☐Angiotensin-converting enzyme inhibitors (captopril, enalapril...)
☐Angiotensin receptor blockers (candesartan, losartan...)
☐Beta-blockers (bisoprolol, carvedilol...)
☐Loop diuretics (furosemide, torasemide...)
☐Thiazide diuretics (hydrochlorothiazide...)
☐Aldosterone antagonist (spironolactone, eplerenone...)
☐Cardiac glycosides (digoxin, digitoxin...)
☐Other (please specify in the box below):

15. Which drug do you add if patients remain symptomatic despite initial therapy?
Please select all items that apply to you.

☐Angiotensin-converting enzyme inhibitors (captopril, enalapril...)
☐Angiotensin receptor blockers (candesartan, losartan...)
☐Beta-blockers (bisoprolol, carvedilol...)
☐Loop diuretics (furosemide, torasemide...)
☐Thiazide diuretics (hydrochlorothiazide...)
☐Aldosterone antagonist (spironolactone, eplerenone...) ☐Quality of life scores
☐Cardiac glycosides (digoxin, digitoxin...)
☐Other (please specify in the box below):

16. Do you prescribe drug treatment to asymptomatic patients?
Please select one item.

☐No
☐Yes
☐Sometimes (please specify in the box below)

17. Which drug do you use for these asymptomatic patients?
Please select all items that apply to you.

☐Angiotensin-converting enzyme inhibitors (captopril, enalapril...)
☐Angiotensin receptor blockers (candesartan, losartan...)
☐Beta-blockers (bisoprolol, carvedilol...)
☐Loop diuretics (furosemide, torasemide...)
☐Thiazide diuretics (hydrochlorothiazide...)
☐Aldosterone antagonist (spironolactone, eplerenone...) ☐Quality of life scores
☐Cardiac glycosides (digoxin, digitoxin...)
☐Other (please specify in the box below):

Feedback and demographic characteristics

18. According to your experience, how would you grade the impact of pharmacological therapy on the course of the disease in your paediatric heart failure patients? (1 no impact, 10 maximal impact)
Please select one item.

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

19. Would you like to add any comment that you consider relevant to this survey?
Please select one item.

☐No
☐Yes (please specify in the box below)

20. How many years of experience do you have caring for children with heart failure?
Please select one item.

☐< 1 year
☐1 to 5 years
☐> 5 to 10 years
☐> 10 years

21. In which type of unit do you work?
Please select one item.

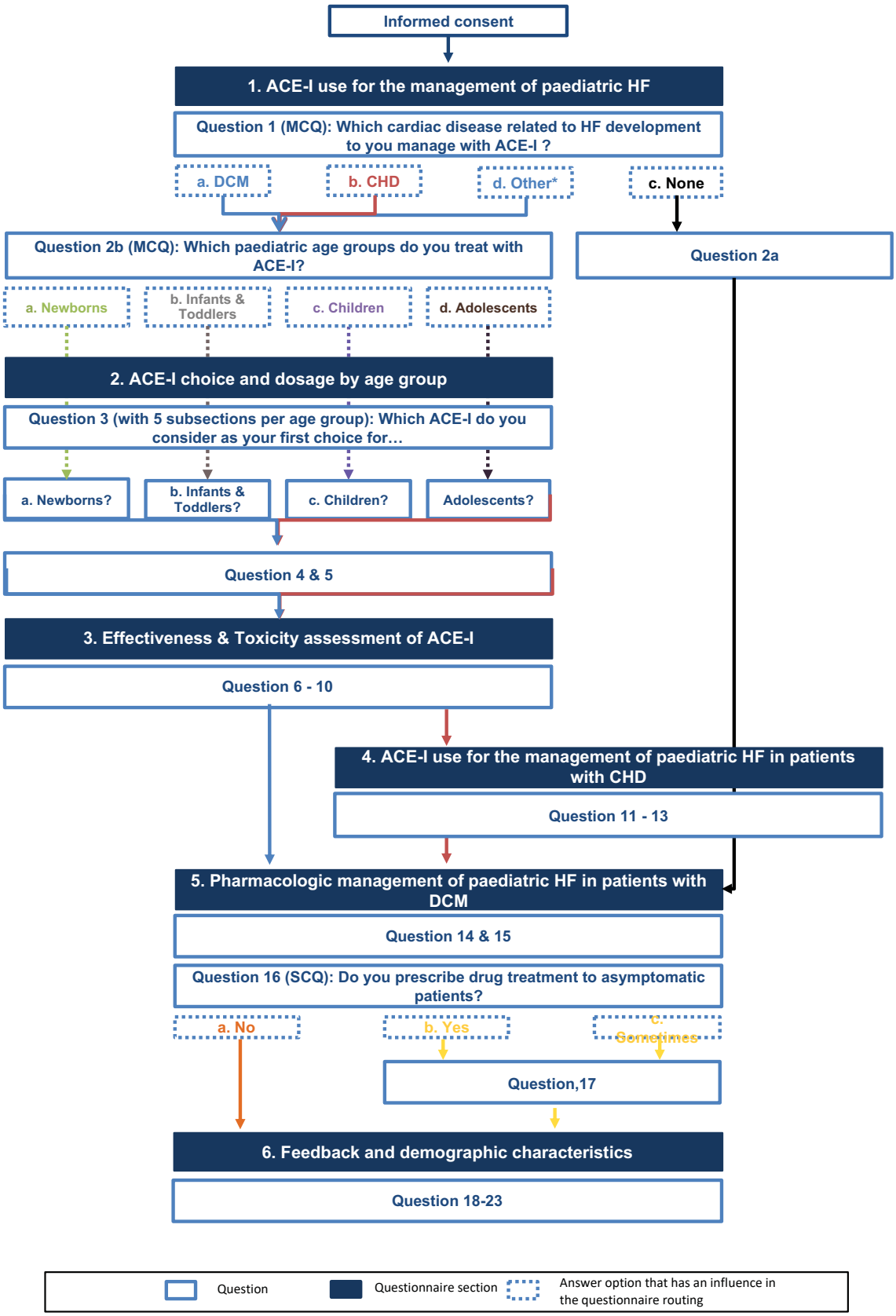
☐Paediatric cardiology
☐Paediatric critical care
☐Neonatology
☐Other (please specify in the box below)

22. How many total paediatric beds (not only in your ward) does the hospital you are working in have?
Please type in in the box below.

23. In which hospital are you working?
This information will only be used to check how many different hospitals and countries contributed to the results. Please remember that all your answers will be reported anonymously.

Name of the hospital	City	Country

Appendix C: Survey study – Questionnaire routing



Appendix D: Survey study - Invitation to participate and reminders

D.1 Invitation e-mail[1]

Labelling of Enalapril from Neonates up to Adolescents

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

We would like to invite you to participate in a **survey** on the **current state of pharmacological management of paediatric heart failure across Europe.** This survey is part of the **LENA** project "**Labelling of Enalapril from Neonates up to Adolescents**" (www.lena-med.eu)**.**

LENA is funded by the European Commission under the Seventh Framework Programme.

Our aim is the development of an oral solid formulation of enalapril appropriate for all paediatric age groups, as well as obtaining data that allow the establishment of evidence based dosing regimens for these patients.

To put LENA into the right context, we need to get information about the different therapeutic strategies currently practiced across Europe. To obtain useful and quality information, it is essential for us to get the best possible representation of centres providing paediatric cardiology care in each country.

In this regard, we would be grateful to count with your collaboration.

The questionnaire will not take more than **15 minutes** of your time and **NO patient data are requested.**

The confidentiality of your personal data is guaranteed. The answers given will be evaluated separately from your personal data and not published in a manner that would permit identification of you, your department or hospital.

Of course you will receive feedback about the survey results as soon as they have been finalised.

If you agree to participate in the survey, please select here

Or copy and paste this address in your browser if selecting above does not work: [DIRECT_ONLINE_LINK]

Please, if possible use **Firefox** or **Google Crome**.

We thank you for your attention and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA investigator
cristina.castro.diez@uni-duesseldorf.de

[1] Invitation e-mail was translated; physicians of German, French, Italian and Spanish speaking countries were approached in their own language. An adapted version was sent to physicians that had previous knowledge about LENA

D.2 Reminder e-mail[1]

Labelling of Enalapril from Neonates up to Adolescents

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

on the xth of January, we requested your collaboration with the **LENA** project "**Labelling of Enalapril from Neonates up to Adolescents**" (www.lena-med.eu) by taking part in a **survey** on the **current state of pharmacological management of paediatric heart failure across Europe.**

Your participation is very important to making the information collected with this survey as valuable as possible. To obtain useful quality information, it is essential for us to get the best possible representation of centres providing paediatric cardiology care in each country.

In this regard, we would be grateful to have your collaboration.

The questionnaire will not take more than **15 minutes** of your time and **NO patient data are requested.**

We would like to remind you that the confidentiality of your personal data is guaranteed. The answers given will be evaluated separately from your personal data and not published in a manner that would permit identification of you, your department or hospital.

If you agree to participate in the survey, please select here

Or copy and paste the following address in your browser if selecting above does not work: [DIRECT_ONLINE_LINK]

Please, if possible, use **Firefox** or **Google Crome**.

If you have any technical difficulty with the link or the web survey tool, please contact us at cristina.castro.diez@uni-duesseldorf.de

We thank you in advance for your collaboration and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA investigator
cristina.castro.diez@uni-duesseldorf.de

[1] Reminder e-mail was translated to German, Spanish and Italian.

D.3 Postal reminder[1]

Mathematisch-Naturwissenschaftliche Fakultät
Institut für Klinische Pharmazie und Pharmakotherapie

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

lena **Labelling of Enalapril from Neonates up to Adolescents**

Prof. Dr. med. Stephanie Läer
Coordinator of LENA
Director of the Institute for Clinical Pharmacy and Pharmacotherapy of the Heinrich-Heine University of Düsseldorf

Tel 0211-8110740
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Stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
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Institute for Clinical Pharmacy and Pharmacotherapy of the Heinrich-Heine University of Düsseldorf

Tel 0211-8110751
Fax 0211-8110741
cristina.castro.diez@uni-duesseldorf.de

Düsseldorf, xx.xx.2015

Heinrich-Heine University
Düsseldorf
Universitätsstraße 1
40225 Düsseldorf
Building 26.22
Floor 02

Dear Dr. X,

On the Xth of January, we requested via e-mail your collaboration with the **LENA project "Labelling of Enalapril From Neonates up to Adolescents"** (www.lena-med.eu) by taking part in a **survey** on the **current state of pharmacological management of paediatric heart failure across Europe.**

We perfectly understand that your daily clinical work does not leave much space in your timetable. At the same time, **your participation is extremely important**, as your data will be an essential contribution to making the information collected with this survey as valuable as possible.

Therefore we would greatly appreciate it if you could take **15 minutes** to answer the questions, keeping in mind that you are **NOT required to provide any specific patient data**.

We would like to remind you that the confidentiality of your personal data is guaranteed. The answers given will be evaluated separately from your personal data and not published in a manner that would permit identification of you, your department or hospital.

If you have any technical difficulty with the web survey tool, or have deleted or not received the link, please contact us at:
cristina.castro.diez@uni-duesseldorf.de

We thank you for your attention and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. med. Stephanie Läer
LENA coordinator

Cristina Castro Díez
LENA investigator

[1] Postal reminder was translated to German and Spanish.

Appendix E: Survey study - Statistical analysis manual

E.1 Table of contents

E.2 Aim of the manual

The manual is intended to provide work description and instructions for the preparation, processing, and analysis of the data that are to be obtained from the European survey on the pharmacological management of paediatric heart failure as part of WP12.

E.3 Tasks and responsibilities

Task Name	Responsible	Deadline*	Current status
Identifying survey participants and its contact data	Castro	May 2014	Done
Developing and designing questionnaire	Castro	25.11.14	Done
Designing questionnaire in web survey tool EvaSys®	Castro	Sep 2014	Done
Performing survey pilot-test	Castro	23.10.14	Done
Running the statistical analysis of the pilot test results	Castro	13.11.14	Done
Preparing manual for statistical analysis	Castro/Khalil	21.11.14	Done
Preparing R® code for analysis of results	Khalil	15.05.15	Done
Performing the survey and collecting its results	Castro	30.04.15	Done
Extracting data from EvaSys® and preparing compilation files	Castro/Khalil	06.05.15	Done
Encoding of data and preparing ready-to-analyse CSV files	Castro/ Makowski	06.05.15	Done
Performing statistical analysis of data in R-Studio®	Khalil	15.05.15	Done
Preparing the survey results report to be included in WP12 final report	Castro	31.10.15	Done

* Deadline dates are illustrative and might be modified during the course of the study

Ip: in process; Nys: not yet started; Sep: September; Tbdn: to be done next

E.4 Overview of data flow

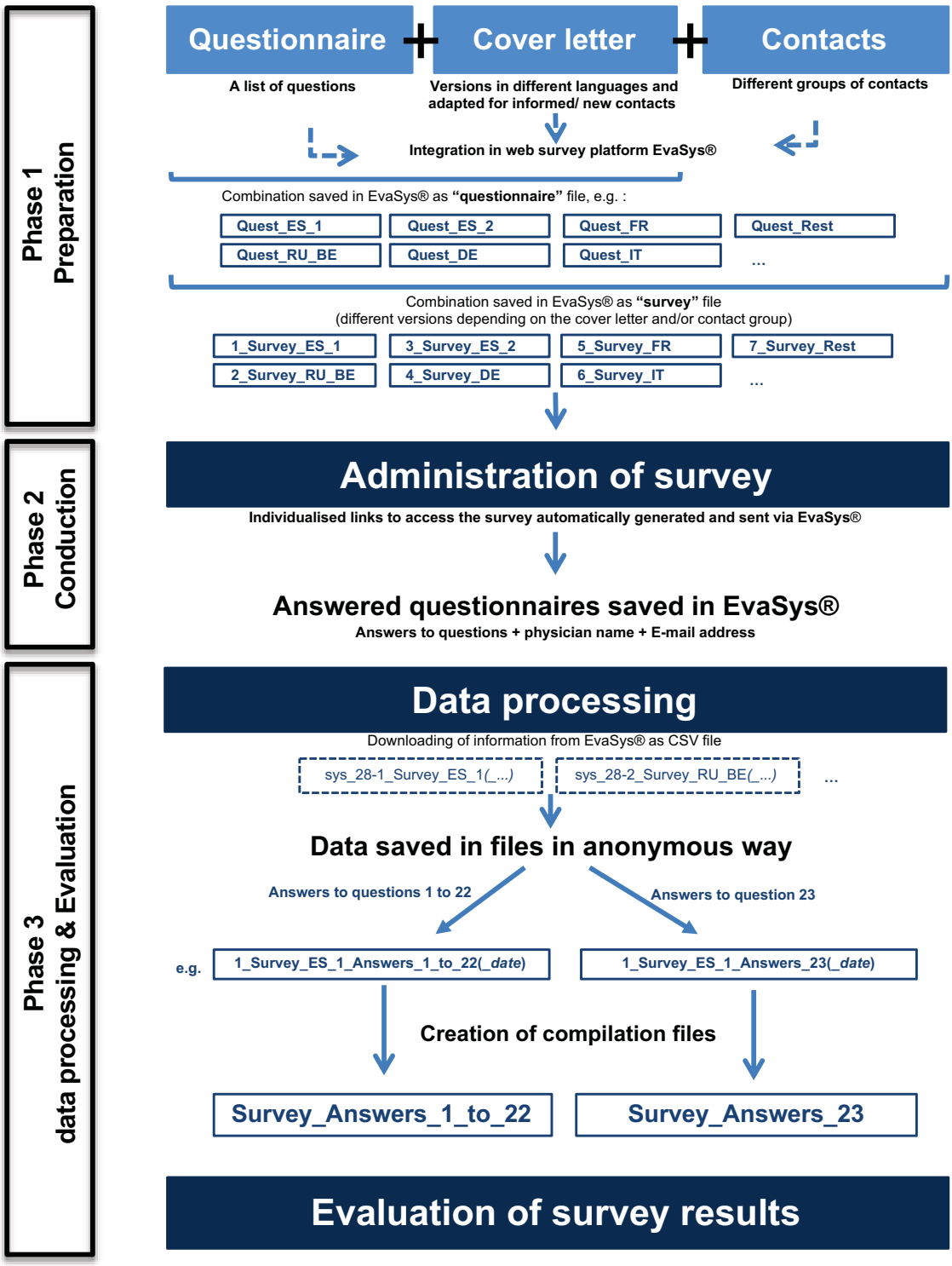


Figure E1. Data flow in WP12 Survey study

E.4.1 Preparation: registration of survey participants in web survey tool EvaSys® and surveys generation

The combination of a questionnaire (containing the questions and the cover letter) and a group of participants are required to create a survey in EvaSys®. Different cover letters have been designed to approach participants depending on their degree of knowledge about LENA when receiving the survey invitation. Furthermore, translations to French, Italian, Spanish and German have been made.

Participants contacts data (physician name and e-mail address) will be entered in EvaSys® under a so-called "Lehrveranstaltung". This can be done via a CSV file or manually. Per each participants group to be entered, a "Lehrveranstaltung" needs to be previously created. EvaSys® will automatically name the later created surveys, after the name of the "Lehrveranstaltung" under which participants are saved. An overview of the nomenclature and content of the different surveys, questionnaires and files of contacts is given in Tables E1 and E2.

Table E1. Details of the components of the different versions of the survey saved in EvaSys® (originally planned)

Survey version name*	Included Questionnaire	Cover letter form	Targeted contact group
1_Survey_ES_1	Quest_ES_1	Spanish for previously contacted	Contacts_ES_1
2_Survey_RU_BE	Quest_RU_BE	English for previously contacted	Contacts_RU_BE
3_Survey_ES_2	Quest_ES_2	Spanish for not previously contacted	Contacts_ES_2
4_Survey_DE	Quest_DE	German for not previously contacted	Contacts_DE
5_Survey_FR	Quest_FR	French for not previously contacted	Contacts_FR
6_Survey_IT	Quest_IT	Italian for not previously contacted	Contacts_IT
7_Survey_Rest	Quest_Rest	English for not previously contacted	Contacts_Rest

Table E2. Details of the imported contact groups

CSV file name	Included contact group
Contacts_ES_1	Physicians working in Spanish hospitals that got information about the survey through the Spanish Paediatric Cardiology Association and contacted us giving their data to participate in the survey
Contacts_RU_BE	Physicians working in Russian and Belgian hospitals that got information about the survey through the national Paediatric Cardiology Association and contacted us giving their data to participate in the survey
Contacts_ES_2	Physicians working in Spanish hospitals not previously aware of the survey, whose contact data where gathered through open sources in internet
Contacts_DE	Physicians working in German, Austrian and German-speaking Swiss hospitals, whose contact data where gathered through open sources in internet
Contacts_FR	Physicians working in French, Monaco and French-speaking Luxembourg and Swiss hospitals, whose contact data where gathered through open sources in internet
Contacts_IT	Physicians working in Italian hospitals, whose contact data where gathered through open sources in internet
Contacts_Rest	Rest of identified participants, whose contact data where gathered through open sources in internet

Additional surveys might have to be created during the study course. For example, if errors in e-mail addresses were detected after the first sending of the web survey link, alternatives for those incorrect contacts will be searched for and approached. New contact files will receive the same name as the original files followed by the word "Error" or "Alternative" (e.g. alternatives to wrong addresses in file *Contacts_ES_2* will be saved as a CSV file named *Contacts_ES_2_Error*). New surveys will be named as the original ones, receiving a correlative number and followed also by the word "Error" or "Alternative" (e.g. *Contacts_ES_2_Error* would belong to *8_Survey_ES_2_Error*).

E.4.2 Conduction

E-mails containing the link to access the survey will be sent via EvaSys®. A unique link will be automatically generated for each participant. The information collected from the returned questionnaires (either fully or partially completed) will be stored in EvaSys®.

E.4.3 Data processing and evaluation

Viewing the data stored in EvaSys® is only possible by downloading it, either as a CSV or a PDF file. These files are named automatically by EvaSys® as *sys_28-* followed by the name of the survey they belong to. As agreed in the procedure plan description for the data protection guarantee of this project only files containing answers in an anonymous way will be used for the processing and evaluation of the data. Thus, the files that are to be directly downloaded from EvaSys®, will only be used with the purpose of creating anonymised files and deleted directly afterwards. Detailed information about the processing and evaluation of the data are provided later on in this document.

E.5 Data processing

The information will be collected and handled according to the procedure plan description for the data protection guarantee of this project, approved by the data protection officer of the Heinrich-Heine University of Düsseldorf by 11th of July 2014. This procedure follows the requirements of the North Rhine-Westphalia Data Protection law, in compliance with the EU Data Protection Directive 95/46/EC.

E.5.1 Data extraction and entry

As above explained, information from the answered questionnaires submitted by participants will be automatically stored in EvaSys®. Files that are to be downloaded from EvaSys® (*sys_28-…*) will only be used with the purpose of creating files containing data in an anonymous way. An example to illustrate structure of *sys_28-…* is provided in **Figure E2**.

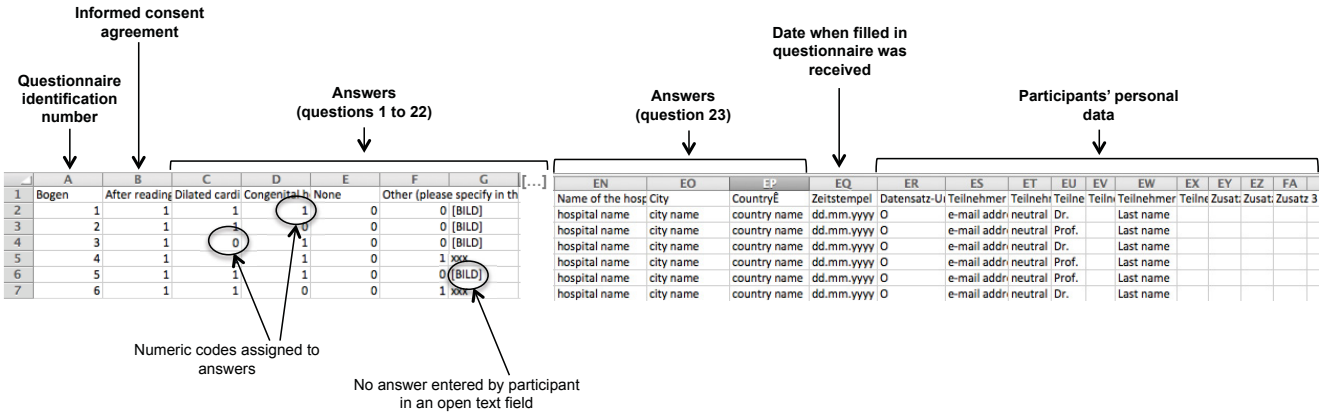


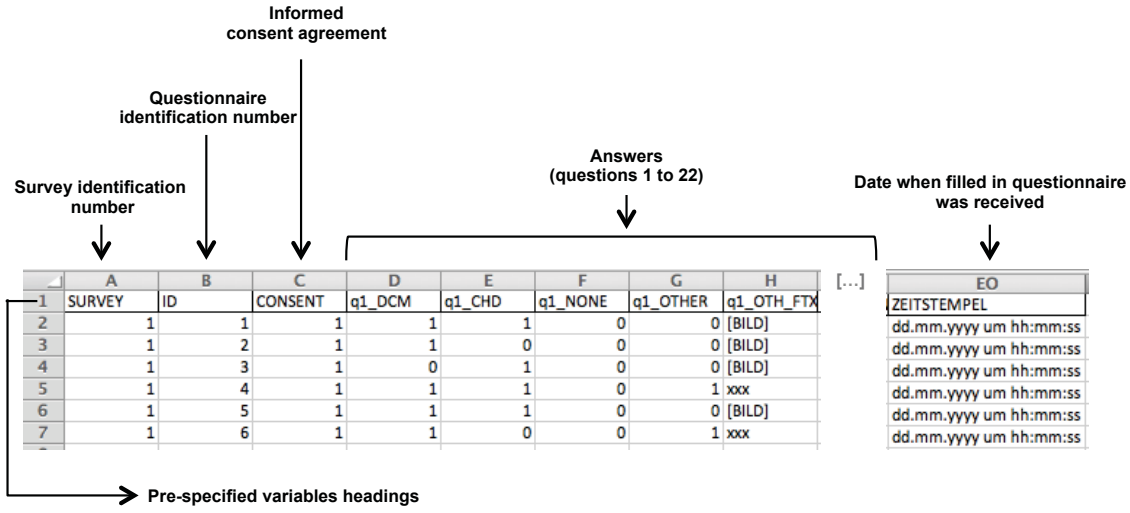
Figure E2. Example CSV file *sys_28-…*

For the creation of the anonymous files physicians' names and e-mail addresses will be deleted and for each survey data will be split in 2 files, one containing answers to questions 1 to 22 and one containing answers to question 23. Files will be regularly downloaded and saved. The files will be named after the survey they are related to, adding to the name the answers they contain and the date (e.g. 1_Survey_ES_1_Answers_1_to_22_2015_02_01, 1_Survey_ES_1_23_2015_02_01). These files will be later on used to create the two anonymised compilation Excel® files that will subsequently be processed to obtain ready-to-analyse data. Nomenclature and description of these two files are provided in **Table E3**.

Table E3. Compilation files

File Name	File Description
Survey_ Answers_1_to_22	Answers given by participants to questions 1 to 22 together with informed consent agreement, survey identification number, questionnaire reference number and date when questionnaire was received.
Survey_Answers_23	Answers given by participants to question 23, section country, survey identification number, questionnaire reference number and date when questionnaire was received.

Before entering the data in the compilation files, an extra column (SURVEY), where the survey identification code will be entered, will be added to each individual file. This will allow the correct identification of each participant (further details under section E.5.2. Nomenclature). In the compilation files the pre-defined variables' names (see **Table E4**), will be entered in the first row before entering data of the individual surveys. Variables' names will be copied from file Coding_system_of_survey_final_version and pasted. The first sheet of the compilation files will contain the raw data with the following structure: survey number will be given in the first column, questionnaire identification number (ID) in the second column and the answers in the subsequent ones. Examples of how these files look like are given in **Figure E3**.



	A	B	C	D	E	F	G	H	[…]	EO
1	SURVEY	ID	CONSENT	q1_DCM	q1_CHD	q1_NONE	q1_OTHER	q1_OTH_FTX		ZEITSTEMPEL
2	1	1	1	1	1	0	0	[BILD]		dd.mm.yyyy um hh:mm:ss
3	1	2	1	1	0	0	0	[BILD]		dd.mm.yyyy um hh:mm:ss
4	1	3	1	0	1	0	0	[BILD]		dd.mm.yyyy um hh:mm:ss
5	1	4	1	1	1	0	1	xxx		dd.mm.yyyy um hh:mm:ss
6	1	5	1	1	1	0	0	[BILD]		dd.mm.yyyy um hh:mm:ss
7	1	6	1	1	0	0	1	xxx		dd.mm.yyyy um hh:mm:ss

Figure E3. Example first sheet of Excel® file *Survey_ Answers_1_to_22*

In further sheets, the data encoding (details under section E.5.2.3. Data encoding system) will be carried out. The last sheet of each file will contain all encoded answers and will be later saved also in CSV format, suitable for the analysis in R-Studio®. CSV files will receive the name of the Excel® file they are related to.

The correct data extraction, entry and encoding will be verified. Procedures will be conducted by 2 persons independently with the help of a checklist (**Appendix E-A**) and then compared, to detect possible inconsistencies.

E.5.2 Nomenclature

E.5.2.1 Questionnaire identification number (ID)

Each of the answered questionnaires submitted by survey participants will be automatically assigned an identification number (bogen number → ID) by EvaSys®. Within each of the created surveys, the first questionnaire will receive the identification number 1 and correlative numbers will be assigned to further questionnaires following a chronological order. Thus, different answered questionnaires will receive the same ID. To allow the correct identification of each questionnaire, as above explained, an extra column containing the survey number will be added to the final individual survey files and entered in the compilation files. With the combination of the survey number and the ID, a new unique reference number for each questionnaire will be created.

E.5.2.2 Survey identification number (SURVEY)

Each survey created will receive a number (see **Table E1**.). As already explained, this number will be entered in column "SURVEY".

E.5.2.3 Data encoding system

Information coming from closed questions is collected by EvaSys® in encoded form as follows:

Single choice: a numeric code is given to each response option.

Multiple choice: each of the single response options presented are encoded as selected (1) or not selected (0).

When the option "other" is selected in a closed question, a box displays where a comment can be entered. Where appropriate, these answers will be grouped into appropriate categories and then encoded following a procedure consistent with the above-mentioned encoding procedure followed by EvaSys®.

Information coming from open questions is collected by EvaSys® in text or numeric form that needs to be later manually encoded. The procedure will be as follows:

Non-numeric open questions: depending on the question, the answers given will be either listed or grouped into appropriate categories. Participants' spelling mistakes will be corrected when necessary for the presentation of data. When grouped, each category will be a new variable. The variable will receive a name consistent with the other answer options provided for the question they belong to and a numeric code will be assigned, mimicking the ones used for multiple or single choice questions, depending on the questions' characteristics.

In the case of multiple-choice questions, for each of the participants having selected "other" a cero or a one will be entered for each of the new created variables.

Numeric open questions: non-numeric characters will be deleted and/or converted into numeric characters. Points will be changed for comas and in case numeric data appear as a date in the Excel® file, answers will be downloaded from EvaSys® in PDF format and the original number recorded will be entered.

Nomenclature of variables is described in **Table E4**. The variables' names start always with a "q" followed by the number of the question they belong to. The five sub-questions that conform question number 3 are named with an "a" for newborns, "b" for infants and toddlers, "c" for children and "d" for adolescents (only question 3a is presented in the table, 3b, 3c and 3d will be encoded resembling the same

procedure). Excel® file *Coding_system_of_survey_final_version* contains all variables names, ready to be copied and pasted for the elaboration of the compilation files.

Table E4. Encoding system

Question	Type of question	Variable name Excel®	Value	Label
-	-	SURVEY	Number 1 to …	-
-	-	ID	Number 1 to ...	-
0	SCQ	CONSENT	1	Selected
			0	Not selected
1	MCQ	q1_DCM	1	Selected
		q1_CHD	0	Not selected
		q1_NONE		
		q1_OTHER		
		q1_ OTHER_FTXT	Free text*	-
2a	MCQ	q2a_NO_EFC	1	Selected
		q2a_HIGH_RISK	0	Not selected
		q2a_NO_CON_FORM		
		q2a_NOT_COMM		
		q2a_OTHER		
		q2a_OTH_FTXT	Free text*	-
2b	MCQ	q2b_NEO	1	Selected
		q2b_INF	0	Not selected
		q2b_CHILD		
		q2b_ADOL		
3	SCQ	q3a1_NEO_ACEI	1	Benazepril
			2	Captopril
			3	Cilazapril
			4	Enalapril
			5	Espirapril
			6	Fosinopril

Question	Type of question	Variable name Excel®	Value	Label
			7	Imidapril
			8	Lisinopril
			9	Moexipril
			10	Perindopril
			11	Quinapril
			12	Ramipril
			13	Trandolapril
			14	Zofenopril
			15	Other
3		q3a1_NEO_OTH_ACEI_FTXT	Free text*	-
3	ONQ	q3a2_NEO_STARTING	Digits given	-
3	ONQ	q3a3_NEO_TARGET	Digits given	-
3	SCQ	q3a4_NEO_FREQ	1	One daily dose
			2	Two daily doses
			3	Three daily doses
			4	Four daily doses
3	MCQ	q3a5_NEO_EXP	1	Selected
		q3a5_NEO_FORM	0	Not selected
		q3a5_NEO_CONV		
		q3a5_NEO_BOOKS		
		q3a5_NEO_PROTOCOLS		
		q3a5_NEO_NO_REASON		
		q3a5_NEO_OTHER		
3		q3a5_NEO_OTH_FTXT	Free text	-
4	MCQ	q4_HOS_PHARMACY	1	Selected
		q4_COMM_PHARMACY	0	Not selected
		q4_PARENTS		
		q4_OTHER		

Question	Type of question	Variable name Excel®	Value	Label
4		q4_OTH_FTXT	Free text	-
5	MCQ	q5_LIQUID	1	Selected
		q5_ CAPSULES	0	Not selected
		q5_ POWDER		
		q5_ OTHER		
5		q5_ OTH_FTXT	Free text	-
6	SCQ	q6_INC_TO_TARGET	1	No
			2	Yes
			3	Sometimes
6		q6_INC_TO_TARGET_FTXT	Free text	-
7	MCQ	q7_CLINICAL_JUD	1	Selected
		q7_ANTICONGESTIVE	0	Not selected
		q7_PARENTS		
		q7_SCORE		
		q7_ECHO		
		q7_NP		
		q7_QOL		
		q7_OTHER		
7		q7_OTH_FTXT	Free text	-
8	SCQ	q8_STOP_CREA	1	1,1 -1,4 times increase in baseline value of creatinine
			2	1,5 - 1,9 times increase in baseline value of creatinine
			3	2,0 -2,9 times increase in baseline value of creatinine
			4	3 or more times increase in baseline value of creatinine
			5	No formal limit
8	SQC	q8_WITHDRAW_CREA	1	1,1 -1,4 times increase in baseline value of creatinine

Question	Type of question	Variable name Excel®	Value	Label
			2	1,5 - 1,9 times increase in baseline value of creatinine
			3	2,0 -2,9 times increase in baseline value of creatinine
			4	3 or more times increase in baseline value of creatinine
			5	No formal limit
8		q8_ADD_COMMENT_FTXT	Free text	-
9	SQC	q9_STOP_HTN	1	Yes
			2	No
9	SQC	q9_WITHDRAW_HTN	1	Yes
			2	No
10	SCQ	q10_TYPE_OF_LIMIT	1	Percentage decrease
			2	Absolute value
			3	Other
10		q10_TYPE_OF_LIMIT_FTXT		
11	MCQ + SCQ	q11_LR_SHUNT	1	Asymptomatic
		q11_P_OVERLOAD	2	Symptomatic
		q11_SV	3	Both
		q11_VR	4	None
11		q11_ADD_COMMENT_FTXT	Free text	-
12	SCQ	q12_ANY_OTHER_CHD	1	No
			2	Yes
12		q12_ANY_OTHER_CHD_FTXT	Free text	-
13	SCQ	q13_TIME_AFTER_SURGERY	1	<1 month
			2	1 to 3 months
			3	3 to 6 months
			4	> 6 months
			5	No use after surgery

Question	Type of question	Variable name Excel®	Value	Label
14	MCQ	q14_ACEI	1	Selected
		q14_ARB	0	Not selected
		q14_BB		
		q14_LOOP		
		q14_THIAZIDE		
		q14_AA		
		q14_CGLYC		
		q14_OTHER		
14		q14_OTH_FTXT	Free text	-
15	MCQ	q15_ACEI	1	Selected
		q15_ARB	0	Not selected
		q15_BB		
		q15_LOOP		
		q15_THIAZIDE		
		q15_AA		
		q15_CGLYC		
		q15_OTHER		
15		q15_OTH_FTXT	Free text	-
16	SCQ	q16_TRT_FOR_ASYM	1	No
			2	Yes
			3	Sometimes
16	OTQ	q16_TRT_FOR_ASYM_FTXT	Free text	-
17	MCQ	q17_ACEI		
		q17_ARB		
		q17_BB		
		q17_LOOP		
		q17_THIAZIDE		
		q17_AA		
		q17_CGLYC		
		q17_OTHER		
17		q17_OTH_FTXT	Free text	-

Question	Type of question	Variable name Excel®	Value	Label
18	SCQ	q18_IMPACT_PHARMACO	1 to 10	-
19	SCQ	q19_ADD_COMMENT	1	No
			2	Yes
19		q19_ADD_COMMENT_FTXT	Free text	-
20	SCQ	q20_YEARS_EXP	1	< 1 year
			2	1 to 5 years
			3	5 to 10 years
			4	> 10 years
21	SCQ	q21_UNIT	1	Paediatric Cardiology
			2	Paediatric critical care
			3	Neonatology
			4	Other
21		q21_UNIT_FTXT	Free text	-
22	ONQ	q22_BEDS_NR	Free text	-
23	OTQ	q23_HOSPITAL	Free text	-
23	OTQ	q23_CITY	Free text	-
23	OTQ	q23_COUNTRY	Free text	-
-	-	ZEITSTEMPLE	Free text	-

E.5.3 Additional rules for data encoding

The answers given by each of the participants will be checked for consistency. Rules to identify and deal with "conflictive" answers are given in **Table E5**.

Table E5. Additional rules for data encoding

Question	"Conflict"	Action
3.1/ 3.5	Although one drug is selected as the ACEI to use in a certain age group, a sentence like „ I actually use drug x and drug y interchangeably as first choice" is given.	The selected drug will be taken in consideration for the analysis. Those cases will be noted and listed separately for later discussion.
3.1/ 3.5	What to do in order not to lose any relevant information in scenarios like: captopril was chosen as the first ACEI choice in infants and toddlers, however, this was accompanied by a comment "I use captopril up to one year of age and then switch to enalapril" is given".	The selected drug will be taken into consideration for the analysis. Those cases will be noted and listed separately for later discussion.
3.2	A dose per day instead of a value of dose per intake is given.	Those answers will be left in blank for analysis.
3.2 and 3.3	An absolute, instead of a mg/kg, dose is given.	Those answers will be left in blank for analysis but noted and listed separately.
3.2 and 3.3	A dose in mg/kg and a maximum absolute dose are given.	Dose per kg will be taken into consideration, unless not compatible with absolute dose.
3.2 and 3.3	A dose range is given.	Three columns will be created to prepare these data for analysis. In the first, the minimum value will be entered, in the second the maximum and the range mid value in the third. The mid-point will be used for the later mean and/or median calculations.
	A dose considered not to be compatible with current knowledge is given.	Doses more than 10 times above what has been published in literature will be excluded from analysis but registered and explicitly noted in a separate table.
	Target dose reported, smaller that starting dose.	Those answers will be left in blank for analysis but noted and listed separately.
8	The same increase in serum creatinine is given for both "stop dose increase" and "withdraw drug therapy" (this does will not include the option "no formal limit").	No special consideration will be made for the data analysis. However, those cases will be noted and listed separately for later discussion, together with the comments given in the box provided under the question.
8	A lower level of serum creatinine deterioration is given for both "stop dose increase" and "withdraw drug therapy".	No special consideration will be made for the data analysis. However, those cases will be noted and listed separately for later discussion, together with the comments given in the box provided under the question.

Question	"Conflict"	Action
15 and 16	The same answer, i.e. drug class, is given for the initial and the add-on therapy. What if all options are identical? What if only one option is the same?	The selected drugs will be taken into consideration for the analysis. Those cases will be noted and listed separately for later discussion.
21	A strong suspicion exists that the number given is the number of paediatric cardiology beds rather than the total number beds in all paediatric wards.	Results will be presented as ranges and all answers given will be taken into consideration.
Applicable to all questions with "other option"	A given comment in free text field is a synonym or could be considered to be one of the given options.	All comments will be initially taken into consideration. However, the adequacy/ consistency with the question will be later discussed. Answers might be re-encoded, but this will be adequately registered.
Applicable to all questions with "other option"	A given comment in free text field is an extra explanation to some other aspect. e.g., In the question "Why do you consider this ACE-I as your first choice?", "others" is clicked and a comment "I use captopril up to one year of age and then switch to enalapril" is given.	Those cases will be noted and listed separately for later discussion. Answers might be re-encoded, but this will be adequately registered.

Decisions made after the discussion of conflictive points will be registered in an Excel file named *Conflictive_answers_codification*.

E.6 Data analysis

E.6.1 Used software tools

The statistical analysis of the data will be performed using R® v.3.2.1 and R-Studio® version 099.465.

E.6.2 Parameters of interest and how results will be reported

The main aims of the study are to describe how ACE-I are being used for the management of heart failure in the paediatric population across Europe, as well as how heart failure due to DCM is being treated in this population. The parameters that may be of interest for each question and how the results will be initially reported are presented below.

Question 1

Which cardiac diseases related to heart failure development do you manage with ACE-I?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and%)
Presentation of results	• Table

Question 2a

Why do you NOT use ACE-I in these paediatric patients?

Type of question	MCQ
Descriptive statistics	• Absolute frequency and relative frequency (number and %)
Presentation of results	• Table

Question 2b

Which paediatric age groups do you treat with ACE-I?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Absolute and relative frequency of the combinations (number and %)
Inferential statistics (*hypothesis/question* and test)	• Significant difference yes vs. no use in newborns? (Binomial test) • Which conditions/aspects are related to the fact that a physician uses ACE-I in newborns? (Fisher test) -Big hospital vs. small hospital -Long vs. short experience in paediatric cardiology -Liquid formulation vs. no liquid formulation -Regions
Presentation of results	• Table

Question 3.1 (a, b, c and d)

Which ACE-I do you consider as your first choice for newborns? Infants and toddlers? Children? Adolescents?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Overlapped bar chart

Question 3.2 (a, b, c and d)

Starting dose in mg/kg per DOSE

Type of question	ONQ
Descriptive statistics	• Mean, range and standard deviation will be calculated for each ACE-I within each age group. (for column starting_min, mid and max separated, even though probably only starting_min will be used)
Presentation of results	• Table • Boxplots

Question 3.3 (a, b, c and d)

Target/Maintenance dose in mg/kg per DAY

Type of question	ONQ
Descriptive statistics	• Mean, range and standard deviation will be calculated for each ACE-I within each age group. (for column target_min, mid and max separated, even though probably only target_mid will be used)
Presentation of results	• Table • Boxplots

Question 3.4 (a, b, c and d)

In how many doses is the target/ maintenance DAILY dose divided?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %) for each of the ACE-I reported within each of the age groups
Presentation of results	• Table • Overlapped bar charts (one chart for each age group)

Question 3.5 (a, b, c and d)

Why is this ACE-I your first choice in newborns? Infants and toddlers? Children? Adolescents?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) of each reason for each ACE-I within each age group. • Absolute and relative frequency (number and %) of the reported arguments (compiling the answers given for all age groups) for making decisions
Presentation of results	• Table

Question 4

Which ACE-I formulation do you prescribe when the adults' formulation is not suitable for a patient?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Absolute and relative frequency (number and %) of the combinations • Absolute and relative frequency (number and %) only one option selected vs. more than 1 option
Presentation of results	• Table

Question 5

What kind of formulation is it?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Absolute and relative frequency (number and %) of the combinations • Absolute and relative frequency (number and %) only one option selected vs more than 1 option (number and%)
Presentation of results	• Table

Question 6

Do you increase the dose of ACE-I to your target, although patient has already improved with a lower dose?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Pie chart

Question 7

How do you assess the effectiveness of ACE-I in your paediatric patients?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table

Question 8

If deterioration of the renal function is detected, which serum creatinine increase relative to baseline value makes you stop increasing the dose of ACE-I? ... withdraw the therapy with ACE-I?

Type of question	SCQ, OTQ
Descriptive statistics	• SCQ: Absolute and relative frequency (number and %) • OTQ: Absolute and relative frequency (number and %) of the different categories
Presentation of results	• Table • Overlapped bars chart

Question 9

If hypotension is detected, do you follow pre-established formal blood pressure limits that make you stop increasing the dose of ACE-I? Do you follow pre-established blood pressure limits that make you withdraw the therapy ACE-I?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Overlapped bars chart

Question 10

What type of limit do you use?

Type of question	SCQ, OTQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table

Question 11

Which of your paediatric patients with congenital heart diseases do you treat with ACE-I?

Type of question	MCQ, SCQ, OTQ
Descriptive statistics	• MCQ: Absolute and relative frequency (number and %) for each of the indications • SCQ: Within each of the indications, absolute and relative frequency (number and %) of the setting in which is used • OTQ: Absolute and relative frequency (number and %) for each of the categories
Presentation of results	• Table • Bar plot

Question 12

Do you use ACE-I for the management of any other congenital heart disease?

Type of question	SCQ, OTQ
Descriptive statistics	• SCQ: Absolute and relative frequency (number and %) • OTQ: Absolute and relative frequency (number and %) for each of the categories
Presentation of results	• Table • Bar chart

Question 13

How long do you treat your patients with congenital heart diseases with ACE-I after heart surgery?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Pie chart

Question 14

Which drug do you use as initial therapy of symptomatic patients who are not dependent on intravenous inotropic/ vasoactive drugs (e.g., dobutamine, milrinone, nitroglycerin, levosimendan...)?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Absolute and relative frequency (number and %) of combinations of drugs used as initial therapy (number of drugs) • Absolute and relative frequency (number and %) of combinations of drugs used as initial therapy (type of drugs) • Absolute and relative frequency (number and %) of type of diuretic therapy used as part of the initial therapy • Consistency between question 14 and 15 will be checked: How many participants gave overlapping answers?
Presentation of results	• Table • Pie chart

Question 15

Which drug do you add if patients remain symptomatic despite initial therapy?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table

Question 16

Do you prescribe drug treatment to ASYMPTOMATIC patients with dilated cardiomyopathy?

Type of question	SCQ, OTQ
Descriptive statistics	• SCQ: Absolute and relative frequency (number and %) • OTQ: Absolute and relative frequency (number and %) for each of the categories
Presentation of results	• Table

Question 17

Which drug do you use for these ASYMPTOMATIC patients?

Type of question	MCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Absolute and relative frequency (number and %) of combinations of drugs used as initial therapy (number of drugs) • Absolute and relative frequency (number and %) of combinations of drugs used as initial therapy (type of drugs)
Presentation of results	• Table

Question 18

According to your experience, how would you grade the impact of pharmacological therapy on the course of the disease in your paediatric heart failure patients?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Bar plot

Question 19

Would you like to add any comment that you consider relevant to this survey?

Type of question	SCQ, OTQ
Descriptive statistics	• SQC: Absolute and relative frequency (number and %) • OTQ: Absolute and relative frequency (number and %) for the grouped categories
Presentation of results	• Table

Question 20

How many years of experience do you have caring for children with heart failure?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table

Question 21

In which type of unit do you work?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table • Pie chart

Question 22

How many total paediatric beds (not only in your ward) does the hospital you are working in have?

Type of question	ONQ
Descriptive statistics	• Intervals and absolute and relative frequency (number and %) of them
Presentation of results	• Table

Question 23

In which hospital are you working?

Type of question	OTQ
Descriptive statistics	• Overall response rate * • Response rate per country* • Absolute and relative frequency (number and %) of participation by region
Presentation of results	• Table • Overlapped bar charts

*The above-mentioned parameters will be calculated separately in Excel (CSV compilation files for analysis in R-Studio® do not contain the information required)

E.6.3 Calculations of the statistical parameters

Percentages will be given without decimal places. Dosage data will be presented with 2 decimal places. Incomplete questionnaires will also be taken into consideration. For each question, calculations will be made considering as total number of subjects the ones to which the question is applicable. Statistical significance will be defined as $p<0,05$. Parameters mentioned in section E.6.2 will be calculated as follows:

Mean

$$\overline{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

Median

If number of values odd

$$M_e = x_{(n+1)/2}$$

If number of values even

$$M_e = (x_{\frac{n}{2}} + x_{\frac{n}{2}+1})/2$$

Response rate

Will be calculated as the number of different hospitals from which at least one physician submits a completed or partially completed questionnaire divided by the number of different hospitals from which a physician is sent the invitation with questionnaire link. Hospitals will be eligible if contact data of at least one clinician dedicated to the field of paediatric cardiology are available. Hospitals will be excluded from the analysis if the clinician contacted expresses his wish not to participate, does not feel able to participate because of limited experience, is retired or the completed questionnaire is returned after the pre-established deadline. If more than one physician in a hospital answered, the first questionnaire received will be taken into consideration for analysis.

E.7 Appendix E-A: Checklist for data extraction and encoding

(Work instructions during creation of encoded compilation files Survey_ Answers_1_to_22 and Survey_Answers_23)

Information of the individual surveys will have been previously downloaded and saved in anonymous way. For this purpose, participants' names and e-mail addresses will have been deleted and files xxx_*Answers_1_to_22* and xxx_*Answers_23* created.

Check if done

1. Column A with survey number entered for each of the individual survey files ☐
2. Duplicated centres deleted (only first questionnaire answered per centre included) ☐
3. Excel® file with the name *Survey_Answers_1_to_22* created ☐
4. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file ☐
5. Data from each individual survey file *xxx_Answers_1_to_22* copied and pasted in the compilation file ☐
6. Variables headings correspond with the entered data ☐
7. In sheet for questions 3.2 and 3.3 codification, variables for minimal, median and maximal dose created for each of the age groups ☐
8. Check consistency question 3.2 y 3.3 (target dose>starting dose) and register it (column consistency, 1 yes, 0 no) ☐
9. Compilation Excel® file *Survey_Answers_23* created ☐
10. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file ☐
11. Hospital name and city deleted in each of t the individual survey files ☐
12. Data from each individual survey file *xxx_Answers_23* copied and pasted in the compilation file ☐
13. Question 1 encoded ☐

14. Question 2a encoded ☐
15. Question 3.1 encoded ☐
16. Question 3.2 encoded ☐
17. Question 3.3 encoded ☐
18. Question 3.5 encoded ☐
19. Question 4 encoded ☐
20. Question 5 encoded ☐
21. Question 6 encoded ☐
22. Question 7 encoded ☐
23. Question 8 encoded ☐
24. Question 10 encoded ☐
25. Question 11 encoded ☐
26. Question 12 encoded ☐
27. Question 14 encoded ☐
28. Question 15 encoded ☐
29. Question 16 encoded ☐
30. Question 17 encoded ☐
31. Question 21 encoded ☐
32. Question 12 encoded ☐
33. All encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_1_to_22* ☐
34. Question 23 encoded (variable for region created) ☐
35. Encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_23* ☐
36. CSV files Survey_Answers_1_to_22 and Survey_Answers_23 created ☐

Further comments:

The content listed above has been checked and is correct

Name, Date, Signature

Appendix F: Survey study- Filled-in and signed checklists for data encoding and extraction

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 1 of 3**

(Work instructions during creation of encoded compilation files Survey_ Answers_1_to_22 and Survey_Answers_23)

Information of the individual surveys will have been previously downloaded and saved in anonymous way. For this purpose participants' names and e-mail addresses will have been deleted and files xxx_*Answers_1_to_22* and xxx_*Answers_23* created.

	Check if done
1. Column A with survey number entered for each of the individual survey files	☑
2. Duplicated centres deleted (only first questionnaire answered per centre included)	☑
3. Excel® file with the name *Survey_Answers_1_to_22* created	☑
4. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file	☑
5. Data from each individual survey file *xxx_Answers_1_to_22* copied and pasted in the compilation file	☑
6. Variables headings correspond with the entered data	☑
7. In sheet for questions 3.2 and 3.3 codification, variables for minimal, median and maximal dose created for each of the age groups	☑
8. Check consistency question 3.2 y 3.3 (target dose>starting dose) and register it (column consistency, 1 yes, 0 no)	☑
9. Compilation Excel® file *Survey_Answers_23* created	☑
10. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file	☑
11. Hospital name and city deleted in each of t the individual survey files	☑
12. Data from each individual survey file *xxx_Answers_23* copied and pasted in the compilation file	☑
13. Question 1 encoded	☑
14. Question 2a encoded	☑

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 2 of 3**

15. Question 3.1 encoded ☑
16. Question 3.2 encoded ☑
17. Question 3.3 encoded ☑
18. Question 3.5 encoded ☑
19. Question 4 encoded ☑
20. Question 5 encoded ☑
21. Question 6 encoded ☑
22. Question 7 encoded ☑
23. Question 8 encoded ☑
24. Question 10 encoded ☑
25. Question 11 encoded ☑
26. Question 12 encoded ☑
27. Question 14 encoded ☑
28. Question 15 encoded ☑
29. Question 16 encoded ☑
30. Question 17 encoded ☑
31. Question 21 encoded ☑
32. Question 12 encoded ☑
33. All encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_1_to_22* ☑
34. Question 23 encoded (variable for region created) ☑
35. Encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_23* ☑

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 3 of 3**

36. CSV files Survey_Answers_1_to_22 and Survey_Answers_23 created ☑

Further comments:

The content listed above has been checked and is correct

Cristina Castro Díez 24.08.2015

Name, Date, Signature

lena	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 1 of 3**

(Work instructions during creation of encoded compilation files Survey_ Answers_1_to_22 and Survey_Answers_23)

Information of the individual surveys will have been previously downloaded and saved in anonymous way. For this purpose participants' names and e-mail addresses will have been deleted and files xxx_*Answers_1_to_22* and xxx_*Answers_23* created.

	Check if done
1. Column A with survey number entered for each of the individual survey files	☑
2. Duplicated centres deleted (only first questionnaire answered per centre included)	☑
3. Excel® file with the name *Survey_Answers_1_to_22* created	☑
4. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file	☑
5. Data from each individual survey file *xxx_Answers_1_to_22* copied and pasted in the compilation file	☑
6. Variables headings correspond with the entered data	☑
7. In sheet for questions 3.2 and 3.3 codification, variables for minimal, median and maximal dose created for each of the age groups	☑
8. Check consistency question 3.2 y 3.3 (target dose>starting dose) and register it (column consistency, 1 yes, 0 no)	☑
9. Compilation Excel® file *Survey_Answers_23* created	☑
10. Pre-specified variables headings entered in the first row of the first sheet of the compilation Excel® file	☑
11. Hospital name and city deleted in each of t the individual survey files	n.a
12. Data from each individual survey file *xxx_Answers_23* copied and pasted in the compilation file	☑
13. Question 1 encoded	☑
14. Question 2a encoded	☑

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 2 of 3**

15. Question 3.1 encoded ☑
16. Question 3.2 encoded ☑
17. Question 3.3 encoded ☑
18. Question 3.5 encoded ☑
19. Question 4 encoded ☑
20. Question 5 encoded ☑
21. Question 6 encoded ☑
22. Question 7 encoded ☑
23. Question 8 encoded ☑
24. Question 10 encoded ☑
25. Question 11 encoded ☑
26. Question 12 encoded ☑
27. Question 14 encoded ☑
28. Question 15 encoded ☑
29. Question 16 encoded ☑
30. Question 17 encoded ☑
31. Question 21 encoded ☑
32. Question 12 encoded ☑
33. All encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_1_to_22* ☑
34. Question 23 encoded (variable for region created) ☑
35. Encoded questions correctly entered in the last sheet of Excel® file *Survey_Answers_23* ☑

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 3 of 3**

36. CSV files Survey_Answers_1_to_22 and Survey_Answers_23 created ☑

Further comments:
Step 11 was not applicable as it has been conducted beforehand by the main researcher. The order of the steps might have been a little different than given here because of the great amount of data. The coding was conducted in several steps. The date below sets the date the of the completion of the data encoding and correction after the comparison of the two ~~ee~~ separately conducted data encoding processes.

The content listed above has been checked and is correct

Nina Makowski, 05.05.2015, Makowski
Name, Date, Signature

Appendix G: Survey study- Data protection procedure plan description

Verfahrensbeschreibung zum Forschungsprojekt:

"Documenting the standard of care of paediatric heart failure across Europe"

Zur Dokumentation beim behördliche Datenschutzbeauftragten nach § 8 Datenschutzgesetzt Nordrhein-Westfalen vom 2000

Verfahrensbezeichnung:

"Documenting the standard of care of paediatric heart failure across Europe"

1. Name und Anschrift der datenverarbeitenden Stelle (§ 3 Abs. 3 DSG NRW, § 2 Abs. 2 DSG NRW)

1.1 Name und Anschrift:

Name:	Heinrich-Heine-Universität, Institut für Klinische Pharmazie und Pharmakotherapie
Straße:	Universitätstrasse 1
Gebäude:	Gebäude 26.22, Ebene 02, Raum 22-24
PLZ:	40225
Ort:	Düsseldorf, Deutschland
Telefon:	
Fax:	
E-Mail:	cristina.castro.diez@uni-duesseldorf.de

1.2 Organizationskennziffer:

Dezernat:	Gebäude 26.22, Ebene 02, Raum 22-24
Institut:	Institut für Klinische Pharmazie und Pharmakotherapie

1.3 Erstellerin des Verfahrensverzeichnisses:

Cristina Castro Díez angeordnet durch Leiterin Prof. Stephanie Läer.

1.4 Findet Auftragsdatenverarbeitung gem. § 11 DSG NRW statt?:

Ja

1.5 Angaben zur Auftragsdatenverarbeitung

Name und Anschrift

Name:	Electric Paper Evaluationssysteme GmbH (EvaSys®)
Straße:	Konrad-Zuse-Allee 13
PLZ:	21337
Ort:	Lüneburg, Deutschland
Telefon:	+49 4131 7360 0 / +49 4131 7360 50
Fax:	+49 4131 7360 60
E-Mail:	info@evasys.de

Daten die technisch gespeichert werden

Namensangaben, Kommunikationsdaten, Berufsdaten (Name des Krankenhauses, Stadt, Land, Jahren von Berufserfahrung, Art der Abteilung, Bettennummer) und Arzneimittelverscheibung Praxis.

Bearbeitungsvorgänge die durchgeführt werden

Erhebung, Speicherung, Analyse

2. Bezeichnung, Zweckbestimmung und Rechtsgrundlage der Datenverarbeitung

2.1 Bezeichnung des Verfahrens

Verarbeitung von dem durch die europaweite Umfrage über die Verschreibung von Arzneimitteln für die Behandlung von Kindern mit Herzinsuffizienz erhobene Daten des Institutes für Klinische Pharmazie und Pharmakotherapie der Universität Düsseldorf. Abkürzung: Umfrage Datenverarbeitung

Es bestehen keine Verknüpfungen zu anderen Verfahrensdataien.

2.2 Zweckbestimmung

Im Rahmen des Projektes werden vor der Umfrage Namensangaben (Anrede, Vorname, Nachname) sowie Kommunikationsdaten (Telefonnummer, E-Mail, Krankenhaus) erhoben. Durch die Umfrage werden Berufsdaten (Name des Krankenhauses, Bettennummer, Art der Abteilung, Stadt, Land, Jahre von Berufserfahrung in der Behandlung von Kindern mit Herzinsuffizienz) und Arzneimittelverschreibung Praxis für die Behandlung von pädiatrische Herzinsuffizienz erhoben.

Die erhobenen Daten werden um die Verschreibung von Arzneimitteln für die Behandlung von Kindern mit Herzinsuffizienz in Europa zu beschreiben benutzt.

1. Namensangaben werden erhoben um die Ärzte an der Teilnahme in der Umfrage einladen zu können.

2. Kommunikationsdaten werden erhoben um die Ärzte an der Teilnahme in der Umfrage einladen zu können.

3. Berufsdaten werden erhoben um zu beurteilen, wie repräsentativ die erhobenen Daten von der echten aktuellen Verschreibung Praxis in Europa sind.

4. Arzneimittelverschreibung Praxis Daten werden erhoben, um die aktuelle europaweit Situation beschreiben zu können.

2.3 Rechtsgrundlage der Datenverarbeitung

Die Rechtsgrundlage wird durch die freiwillige, informierte Einwilligung der Studienteilnehmer nach § 28 Absatz 2 gewährleistet.

Die personenbezogenen erhobenen Daten werden nur während der Dauer der Umfrage (6 Monaten) behalten. Die Antworten werden für die Analyse von den personenbezogenen Daten getrennt und nach der genannten Zeit werden die anonymisiert. Die nicht-anonymisierte erste Datenverarbeitung ist für

diese Studie am Besten geeignet. Dadurch wird sich die Beurteilung von der Repräsentativität der Antworten von der echte europaweite Situation ermöglichen.

Diese Vorgehensweise kann als sicher gehalten werden, da die Schutzwürdigkeit der Daten aus folgenden Gründen als gering beurteilt werden kann:

Das Verstößen gegen der Sicherheit der personenbezogene gespeicherten Daten kaum gesetzliche oder moralische Konsequenzen für die betroffenen haben würden.

Eine Beeinträchtigung des Informationellen Selbstbestimmunsgrecht durch den einzelnen als tolerable bezeichnet werden kann.

Eine Beeinträchtigung der persönlichen Unversehrtheit nicht möglich scheint.

Um die Verweigerungsrate zu vermindern, und nach die unter §4 Abs. 1 der DSG NRW berücksichtigte Umstände, wird die Einwilligung elektronisch erklärt. Auf Grund der Schutzwürdigkeit der verarbeitende Daten, kann diese Vorgehensweise für ausreichend gehalten werden.

2.4 Werden automatisierte Einzelentscheidungen getroffen?

Nein

3. Art der gespeicherten Daten

Handelt es sich um besondere sensitive Daten gem. § 4 Abs. 3 DSG NRW?

Namensangaben:	Nein
Kommunikationsdaten:	Nein
Berufsdaten:	Nein
Arzneimittelverscheibung Praxis:	Nein

4. Schutzbedarf und Grundwerte

4.1 Risikoabschätzung

Qualitative Bewertung der Gefährdung der Grundwerte mit einer 3-stufigen Skala (normal, hoch, sehr hoch).

Namensangaben:	Normal
Kommunikationsdaten:	Normal
Berufsdaten:	Normal
Arzneimittelverscheibung Praxis:	Normal

Allgemeine Begründungen:

Man kann von einer sehr geringen bis normales Schutzbedarfkategorie ausgehen, weil:

Das Verstößen gegen der Sicherheit der personenbezogene gespeicherten Daten kaum gesetzliche oder moralische Konsequenzen für die betroffenen haben würde.

Eine Beeinträchtigung des Informationellen Selbstbestimmungsrecht durch den einzelnen als tolerable bezeichnet werden kann.

Eine Beeinträchtigung der persönlichen Unversehrtheit nicht möglich scheint.

Die Vertraulichkeit, Verfügbarkeit und Integrität werden durch organisatorische und technische Maβnahmen gewährleistet.

5. Kreis der Betroffenen

Ärzte die in Europa im Rahmen pädiatrische Kardiologie in Krankenhäusern berufstätig sind.

6. Art regelmäßig zu übermittelnder Daten sowie deren Empfänger und Art und Herkunft regelmäßig empfangener Daten

6.1 Art regelmäßig zu übermittelnder Daten sowie deren Empfänger

Keine.

6.2 Art regelmäßig empfangener Daten sowie deren Herkunft

Keine.

7. Zugriffsberechtigten Personen oder Personengruppen

Der Projektbeteiligte in dem Institut für Klinische Pharmazie und Pharmakotherapie.

8. Technische und organisatorische Maßnahmen

Die dazugehörige Maßnahmen werden beim Electric Paper Evaluationssysteme GmbH (EvaSys®) angewendet, wie in dem unterschriebenen Vertrag mit der Heinrich-Heine-Universität Düsseldorf vereinbart.

9. Technik des Verfahrens

9.4 Eingesetzte Software (einschl. Standardvefahren)

EvaSys® Version 6.0

Excel® (nur anonymisierte Daten werden in diesem Software eingetragen).

SPSS® (nur anonymisierte Daten werden in diesem Software eingetragen).

10. Fristen für die Berichtigung, Sperrung und Löschung gem. (§ 19 Abs. 1, 2 und Abs. 3 DSG NRW)

Frist für die Berichtigung (§ 19 Abs. 1 DSG NRW)

6 Monate (Umfrage Dauer, danach werden personenbezogenen Daten gelöscht).

Frist für die Sperrung (§ 19 Abs. 2 DSG NRW)

6 Monate (Umfrage Dauer, danach werden personenbezogenen Daten gelöscht).

Frist für die Löschung (§ 19 Abs. 3 DSG NRW)

Die Löschung der Daten wird nach direktem Wunsch eines Teilnehmers geschehen. Die Löschung der Daten wird spätestens nach Beendigung der Umfrage gemacht (6 Monate nach Anfang der Umfrage). Nach der Empfehlungen der Deutschen Forschungsgemeinschaft, werden die Originaldaten in der Institution für einen Zeitraum von 10 Jahren gespeichert, aber nur in anonymisierter Form.

11. Beabsichtigte Datenübermittlung an Drittstaaten (§ 17 DSG NRW)

Es wird keine Datenübermittlung an Drittstaaten stattfinden.

12. Organisation und Infrastruktur § 10 Abs. 3 DSG NRW

Siehe Anlage I.

13. Abschließende Bewertung des Fachbereichs

(Separates Dokument: Abschließende datenschutzrechtliche Stellungnahme)

14. Ergänzungen (Gewährleistet das Verfahren die Rechte der Betroffenen auf Auskunft, Widerspruch, Unterrichtung, Berichtigung, Sperrung und Löschung nach § 5 DSG NRW?)

Siehe Punkt 10.

Jeder Teilnehmer wird zu Beginn der Teilnahme an der Umfrage die erforderliche Information durch die Einwilligungserklärung (Anlage II) erhalten.

15. Ergebnis[1]

Ergebnis der Vorabkontrolle durch den behördlichen/betrieblichen DSB

Das Verfahren wird der Schutzstufe NORMAL zugeordnet.

(x) Die technischen und organisatorischen Maβnahmen des Verfahrens sichern die Vertraulichkeit, die Integrität und die Verfügbarkeit der Daten des Betroffenen.

(x) Das Restrisiko ist tragbar.

( ) Die technischen und organisatorischen Maβnahmen des Verfahrens sichern die Vertraulichkeit, die Integrität und die Verfügbarkeit der Daten des Betroffenen nur unzureichend.

( ) Es sind folgende Maβnahmen zum Schutz der Grundwerte zu ergreifen:

07.07.2014

Das Verfahrensverzeichnis ist in Ordnung.

Es bestehen keine durchgreifenden datenschutzrechtlichen Bedenken gegen die Durchführung Ihres Projektes.

Bezgl. der eingesetzten Befragungssoftware EvaSys® sind allerdings noch einige technische und organisatorische Mängel zu beanstanden.

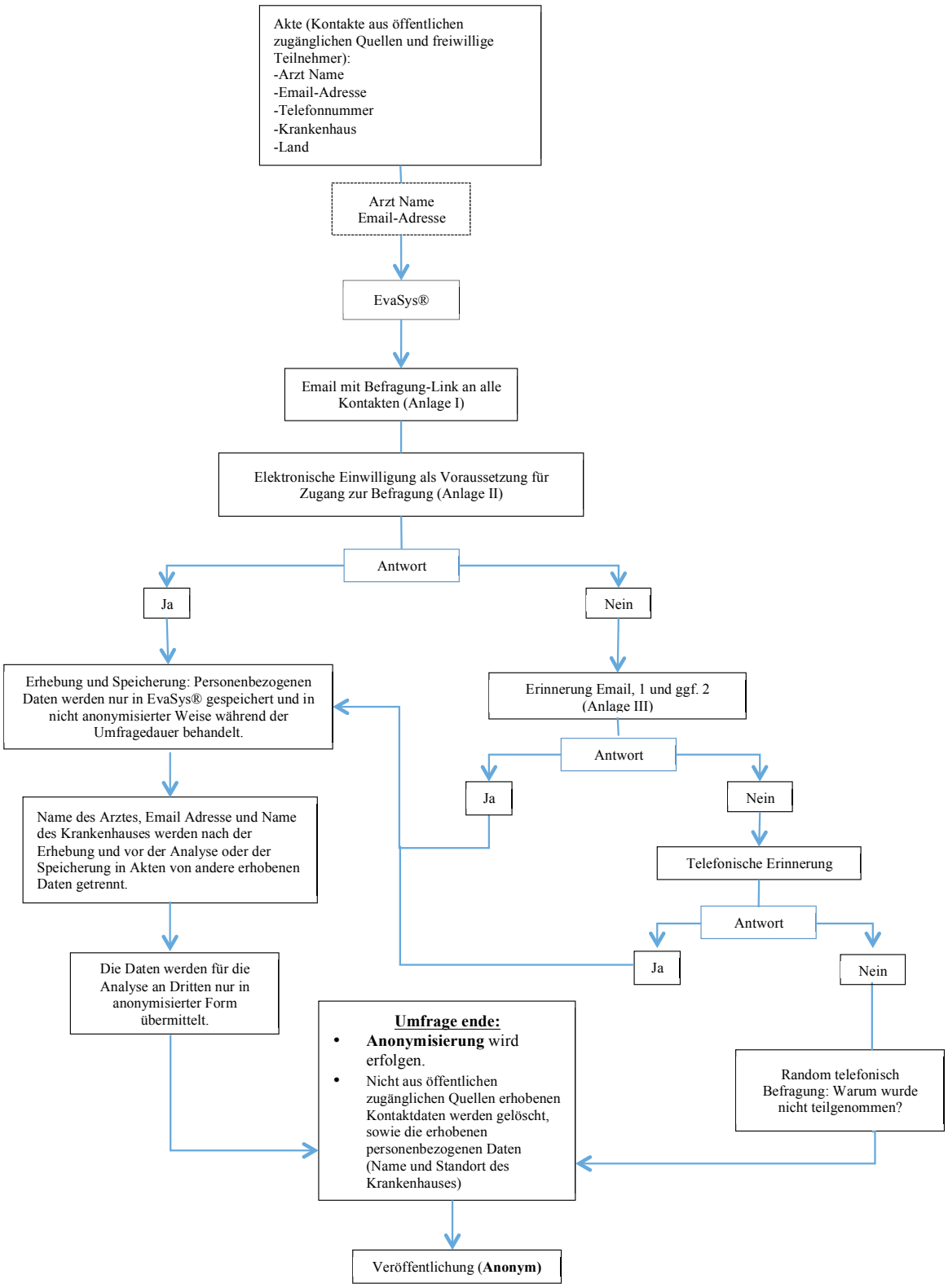
Das zur Erhebung der Umfragedaten verwendete System EvaSys® befindet sich derzeit noch in der datenschutzrechtlichen Vorabkontrolle, die im Rahmen eines anderen Projektes durchgeführt wird. Auf

[1] Ab diesem Punkt würde die Information vom Datenschutzbeauftragten ausgefüllt.

Grund der Schutzbedürftigkeit der Daten im Projekt LENA ist es aber vertretbar, das Projekt LENA bereits vor der absehbaren datenschutzrechtlichen Abnahme des Systems EvaSys® durchzuführen. Für das FP LENA ergeben sich hieraus zunächst keine weiteren datenschutzrechtlichen Auflagen.

Anlage I: Organisation und Infrastruktur § 10 DSG NRW

1. Flussdiagram



2. Durchführung

Die Ausführung der Vorschriften des Datenschutzgesetzes Nordrhein-Westfalen wird durch folgende technische und organisatorische Maßnahmen sichergestellt:

EvaSys® technische und organisatorische Maßnahmen (die dazugehörige Maßnahmen werden beim Electric Paper Evaluationssysteme GmbH EvaSys® angewendet, wie in dem unterschriebenen Vertrag mit der Heinrich-Heine-Universität Düsseldorf vereinbart).

Alle Betroffenen werden mit einer Einwilligungserklärung informiert und diese als Voraussetzung für die Teilnahme an der Umfrage zustimmen müssen.

Nur die genannten Zugriffsberechtigten Personen werden in der verantwortlichen Stelle das Passwort um Zugang zu den im EvaSys® erhobenen Daten haben.

Die erhobenen Daten werden nach dem Empfang und vor der Analyse oder Speicherung in Akten aufgenommen. Dabei werden der Name des Arztes, die zugehörige Email-Adresse und der Name des Krankenhauses von anderen Daten getrennt. Nach der Beendigung der Umfrage werden die Daten anonymisiert, das heißt, die EvaSys® Datei die eine Zuordnung der Antworten zu einer Person ermöglichen würde, wird gelöscht.

Appendix H: Survey study- Data Protection Officer approval

Der Datenschutzbeauftragte

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

11. Juli 2014

Abschließende datenschutzrechtliche Stellungnahme

Elektronische Umfrage zur Pharmakotherapie der pädiatrischen Herzinsuffizienz in Europa – Studie im Rahmen des europäischen Forschungsprojektes LENA

Vorbemerkung:

Der Datenschutzbeauftragte der Heinrich-Heine-Universität Düsseldorf ist am 16. April 2014 von Frau Prof. Dr. med. Läer gebeten worden eine datenschutzrechtliche Stellungnahme zum oben genannten Forschungsvorhaben abzugeben.

Zu diesem Zweck war die Bereitstellung zahlreicher Dokumente über den Inhalt sowie die Art und Weise der Durchführung der Studie sowie die Darstellung der Notwendigkeit zur Erhebung und Verarbeitung personenbezogener Daten der teilnehmenden Personen notwendig.

Die Leiterin der Studie Frau Prof. Dr. Läer und ihre Mitarbeiterinnen Frau Cristina Castro Diez wurden allgemein über die datenschutzrechtlichen Grundlagen wissenschaftlicher Forschung und speziell über die aus Sicht des Datenschutzrechtes NRW notwendigen Änderungen im Aufbau und Ablauf der Studie beraten.

Ergebnisse:

1. **Verantwortliche Stelle:**

   Verantwortliche Stelle der Umfrage ist das Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf unter Leitung von Frau Prof. Dr. med. Läer.

2. **Erforderlichkeit der Datenerhebung und Verarbeitung (Rechtsgrundlagen):**

   Zur Durchführung der Umfrage werden von Ärzten, die in europäischen Kinderkrankenhäusern arbeiten, email Adressen aus dem Internet extrahiert. Die Ärzte werden

dann über ein Befragungsportal zu einer elektronischen Umfrage (Arzneimittelgebrauch für bestimmte Medikamente in ihrem Krankenhaus) eingeladen. In die elektronische Umfrage können die Ärzte einwilligen und allgemeine Informationen zum Arzneimittelgebrauch ihres Krankenhauses angeben.

Die Erhebung der Kontaktdaten aus öffentlichen Quellen zum Zwecke der Kontaktaufnahme ist datenschutzrechtlich unbedenklich. Nach erfolgreicher Kontaktaufnahme und erfolgter Einwilligung werden von den Teilnehmern selbst die für die Studie notwendigen Daten in das Befragungsportal eingegeben. Die so erhobenen personenbezogenen Daten (Name, Kontaktdaten, Berufsdaten und die Praxis der Arzneimittelverschreibung) sind zur Durchführung der Umfrage notwendig und geeignet.

Der Inhalt des vorgelegten Fragebogens selbst ist nicht zu beanstanden.

Die Notwendigkeit des Umfangs der Datenerhebung und der anschließenden Verarbeitung entsprechen insofern den Bestimmungen der Datenverarbeitung für wissenschaftliche Zwecke gemäß § 28 DSG NRW.

3. <u>Freiwilligkeit und Informierte Einwilligung:</u>

Die Teilnehmer an der Umfrage werden umfassend über Inhalt, Zweck und Ablauf der Studie informiert. Sie werden über die jederzeit bestehende Möglichkeit der Beendigung der Teilnahme ohne Angaben von Gründen und negative Konsequenzen informiert. Die Teilnehmer willigen der Speicherung und Verarbeitung ihrer Daten elektronisch ein, wobei die elektronische Einwilligung durch ein opt-in (die Interessenten müssen die Teilnahme an der Studie explizit bestätigen) realisiert wird. Hier wird zwar empfohlen, die elektronische Einwilligung durch ein double-opt-in oder zumindest durch ein confirmed opt-in zu ermöglichen, es bestehen aber keine durchgreifenden datenschutzrechtlichen Bedenken zur der hier gewählten Einwilligungslösung.

4. <u>Datensparsamkeit:</u>

Die Datensparsamkeit ist insofern gegeben, als nur die notwendigen und geeigneten personenbezogenen Daten erhoben und verarbeitet werden und die Anonymisie-

rung gemäß § 28 Abs. 3 DSG NRW so früh wie möglich erfolgt, spätestens nach Auswertung der Umfragedaten nach ca. 6 Monaten.

5. Verfahrensverzeichnis und Datensicherheit (technische und organisatorische Maßnahmen):

Der nach § 8 DSG NRW erforderliche Eintrag in das Verfahrensverzeichnis der Heinrich-Heine-Universität Düsseldorf wurde abschließend erstellt.

Die Durchführung der Umfrage erfolgt mit Hilfe des an der Heinrich-Heine-Universität Düsseldorf bereits eingesetzten Befragungssystems EVAsys, welches sich derzeit allerdings noch in der datenschutzrechtlichen Vorabkontrolle gemäß § 10 DSG NRW befindet, die im Rahmen eines anderen Projektes durchgeführt wird. Auf Grund der Schutzbedürftigkeit der hier erhobenen Daten ist es aber vertretbar, das Projekt bereits vor der absehbaren datenschutzrechtlichen Abnahme des Systems EVAsys durchzuführen. Für die hier vorgesehene Umfrage ergeben sich hieraus zunächst keine weiteren datenschutzrechtlichen Auflagen.

Das wissenschaftliche Team der Studie übernimmt aus dem System Evasys nur die für die Analyse notwendigen Umfrageantworten auf die eigenen Notebooks. Alle personenbezogene Daten wie Kontaktdaten, Name und Standort des Krankenhauses verbleiben auf dem Befragungssystem EVAsys. Die Auswertung der Umfrageantworten erfolgt auf den Notebooks mit Hilfe von MS Excel und SPSS. Ohne Kenntnis der auf dem Befragungssystem EVAsys verbliebenen personenbezogenen Daten kann den auf die Notebooks übernommen Daten keine konkrete Person zugeordnet werden. Insofern wurde für die Verarbeitung der (Analyse-)Daten auf besondere Sicherheitsmaßnahmen, wie z.B. Verschlüsselung der Daten auf den Notebooks verzichtet.

6. Anonymisierung und Pseudonymisierung

Eine Trennung der personenbezogenen Daten von den Umfrageantworten findet gemäß des Ablaufplans der Untersuchung nur insofern statt, als dass die Umfrageantworten zum Zwecke der Auswertung von EvaSys auf die von den Wissenschaftlern benutzten Notebooks übertragen werden

Eine Anonymisierung findet erst nach Auswertung der Umfrage statt, d.h. die nur noch auf dem Befragungssystem EVAsys vorhandenen personenbezogene Daten wie Kontaktdaten, Name und Standort des Krankenhauses werden unwiderruflich gelöscht.

Diese Vorgehensweise ist durch § 28 Abs. 1 Satz 3 DSG NRW (Datenverarbeitung für wissenschaftliche Zwecke) gedeckt, da der Personenbezug auf dem System EVAsys gelöscht wird, sobald der Forschungszweck dies gestattet. Die Anonymisierung erfolgt zwar laut Flussdiagramm erst nach der Analyse, dies ist aber auf Grund des Schutzbedarfes der Daten und der Tatsache, dass die personenbezogenen Daten spätestens nach 6 Monaten gelöscht werden datenschutzrechtlich zu vertreten.

7. Zweckbindung

Die erhobenen personenbezogenen Daten dürfen nur für den Zweck dieser Studie verwendet werden. Weitergehende Forschungen mit den gesammelten Daten benötigen eine erneute informierte Einwilligung der Betroffenen.

8. Löschung und/oder Sperrung der Daten:

Alle personenbezogenen Daten werden laut Flussdiagramm nach der Auswertung (6 Monate) gelöscht.

9. Übermittlung an Dritte:

Übermittlungen an Dritte erfolgen nicht.

Fazit:

Es bestehen keine durchgreifenden datenschutzrechtlichen Bedenken gegen die Durchführung des Projektes.

Mit freundlichen Grüßen

gez. Kurt Finkbeiner

Appendix I: Ethics Committee approval

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF
ETHIKKOMMISSION der Medizinischen Fakultät

ETHIKKOMMISSION der Medizinischen Fakultät der Heinrich-Heine-Universität, Moorenstr. 5, 40225 Düsseldorf

Frau
Prof. Dr. med. Läer
Institut für Klinische Pharmazie und Pharmakotherapie

HIER

Prof. Dr. T. Hohlfeld

Telefon: (0211)81-19590
Sekretariat: (0211)81-19591
FAX: (0211)81-19592
Ethikkommission@med.uni-duesseldorf.de

08. Aug. 2014

Stets angeben:
Studiennummer: 4771

Sehr geehrte Frau Kollegin Läer,

die Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf hat Ihren Antrag mit dem Titel:

Electronic survey on the standard of care for children with heart failure across Europe

geprüft und beurteilt.

Von Seiten der Kommission bestehen keine ethischen oder rechtlichen Bedenken gegen die Durchführung der elektronischen Umfrage.

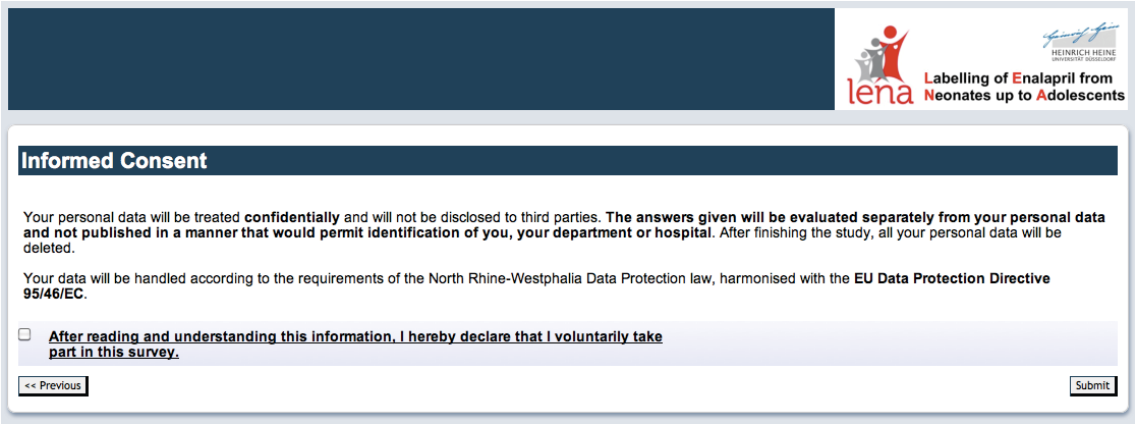
Nach Abschluss des Projektes bitte ich um Übersendung eines knappen Schlussberichtes oder einer abschließenden Publikation.

Für die Durchführung der Studie wünschen wir viel Erfolg!

Mit freundlichen Grüßen

Prof. Dr. Klaus-Dietrich Kröncke
i. A. der Kommission

Appendix J: Survey study - Informed consent



Appendix K: Delphi study – Invitation for expert panel recruitment

Labelling of Enalapril from Neonates up to Adolescents

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

We would like to invite you to participate in a **Delphi study** on the **pharmacotherapeutic management of paediatric heart failure**. This study is part of the **LENA** project **"Labelling of Enalapril from Neonates up to Adolescents"** (www.lena-med.eu), funded by the European Commission under the Seventh Framework Programme.

As you are aware of, little evidence is currently available regarding the pharmacotherapeutic management of paediatric heart failure. Thus, therapeutic strategies are largely supported by adults' data extrapolation and own expertise.

A Europe wide survey recently carried out among paediatric cardiologists as part of LENA has revealed a wide variability in drug treatment routines across Europe.

Thus, as a further step we would like to conduct a discussion on these controversial aspects through a Delphi process. In this regard, **we would appreciate it very much if we could count with your valuable collaboration, knowledge and experience.**

The Delphi method is designed as a group communication process, which aims to achieve a convergence of opinion on a specific issue.

Experts are asked to fill in questionnaires in an iterative process, rating items and giving arguments for the answers given. After each round, an anonymous summary of the participant's opinion from the previous round as well as the reasons they provided for their judgments is passed to all participants. Thus, experts are encouraged to revise their earlier answers in light of the replies of other members of their panel.

We are convinced that the findings of this discussion will shed light on this important topic and place the focus on relevant issues that need the attention of the scientific community.

The study will be conducted **on-line** between **July and August 2015** and will be conformed by **2 rounds**. In order to maintain the dynamism of the process, participants will be asked to return the filled in questionnaires within one week. These will contain **16 questions** and completing them will not take more than **15 minutes** of your time.

The confidentiality of your personal data is guaranteed. The answers given will not be published in a manner that would permit identification of you or your institution.

If you agree to participate, please give us a short reply. We will send you the questionnaire link next week to this e-mail address.

We thank you in advance for your collaboration, and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA research assistant
cristina.castro.diez@uni-duesseldorf.de

Appendix L: Delphi study – Background for statements presentation

Statements		Background	
		Summary of survey results as basis of the topics addressed	Selection and framing of statements
Considerations for optimal ACE-I dosage			
1	There is a need for clear monitoring schedules for the early detection of acute kidney injury in paediatric patients on ACE-I therapy.	• 25% of participants reported not following any specific criterion to decide when to stop increasing ACE-I dose and/or withdraw therapy when deterioration of the renal function is detected. • Disparity in the cut-off values selected by those that base decisions on a formal limit. • Only 29 out of 100 participants reported following a formal blood pressure cut-off value to decide when to withdraw ACE-I if hypotension develops in the context of the therapy.	Little specific guidance has been published (Kantor et al., 2013; Taketomo et al., 2014), poor description of criteria followed in most of paediatric heart failure studies.
2	There is a need for clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.		
3a	In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.	• Wide variability in the starting and maintenance ACE-I doses in use reported to treat heart failure in children.	Due to the complexity of the topic, discussion about adequate dosing schedules of the different ACE-I in the different age groups was out of the scope of this study. Two general criteria that might serve as staring points in the achievement of standard dosing criteria were identified. The supplement table of the paediatric guideline elaborated by the Canadian Cardiovascular Society (Kantor et al., 2013) recommends increasing the captopril dose every 48h. This is the shortest suggested interval identified in the literature for ACE-I up-titration in paediatric patients with heart failure. The ESC guideline for the management of heart failure in adults (McMurray et al., 2005) recommends doubling the dose at each step during up-titration in the therapy of heart failure.
3b	In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.		

Statements		Background	
		Summary of survey results as basis of the topics addressed	Selection and framing of statements
4	If deterioration of the renal function occurred in a patient on ACE-I therapy, concomitant diuretic medication should be readjusted before deciding to down titrate/ stop up-titrating the ACE-I.	• Participants repeatedly commented on the influence of concomitant diuretic therapy in the strategy to be best adopted when deterioration of renal function develops in the context of ACE-I.	ESC guideline for the management of heart failure in adults (McMurray et al., 2005) recommends considering first reducing the dose of diuretics, if no signs of congestion exist, when deterioration of renal function is detected in patients on ACE-I.
5	If no adverse events occur, ACE-I dose should be increased to the target dose, even if the patient has already experienced improvement with a lower dose.	• Division of opinion on how to establish optimal ACE-I maintenance dose: 42% aim for target dose, 45% stop when improvement is observed.	ESC guideline for adults recommends aiming "for target dose or, failing that, the highest tolerated dose" (McMurray et al., 2005) These target doses are those that were used and showed an improvement in survival and hospitalizations in key randomized trials. Evidence in adults suggests that clinical symptoms appear to be inadequate in determining optimal ACE inhibitor dose level (López-Sendón et al., 2004).
6	In order to maximise the accuracy of the ACE-I dose given, the use of different types of formulations for a patient throughout the duration of the treatment should be avoided.	• Half (47%) of the respondents indicated that the ACE-I formulations they prescribe are provided to their patients from more than a single source.	As no licensed paediatric appropriate formulation is commercialised in Europe, pharmacies provide formulations individually prepared for the patients under prescription. It has been documented that a wide variety of unlicensed and untested ACE-I formulations, with no proven bioequivalence, are used interchangeably in Europe (Mulla et al., 2007; Pabari et al., 2012). Sometimes parents have to crush tablets and dissolve or disperse them for administration to their child. It is not possible to be confident that the rate and extent of ACE-I absorption do not vary according to its formulation.

Statements		Background	
		Summary of survey results as basis of the topics addressed	Selection and framing of statements
ACE-I for the management of congenital heart diseases			
7	Paediatric patients with asymptomatic mitral or aortic regurgitation benefit from ACE-I therapy	• 92 of the participating physicians reported using ACE-I to treat patients with valve regurgitation; 33 treat only symptomatic patients, 44 both symptomatic and asymptomatic and 15 reported using them only for asymptomatic patients. In summary, approximately one third of these participants reported not using ACE-I to treat asymptomatic patients with valve regurgitation.	Hemodynamic benefits of ACE-I have been observed in children with valve regurgitation in some small experimental studies (Alehan and Ozkutlu, 1998; Calabrò et al., 1999; Mori et al., 2000), all of which included only patients with no heart failure symptoms.
8	Paediatric patients with pressure overload lesions should be routinely prescribed ACE-I.	• Half of the participants reported using ACE-I in the context of pressure overloading lesions.	ISHLT Practice Guidelines for Management of Heart Failure in Children (Rosenthal et al., 2004) stated "In pressure-induced left ventricular hypertrophy, with normal myocardial function, ACE inhibitors are not recommended in the absence of a non-cardiac indication such as hypertension. (Level of Evidence C; Strength of Recommendation III)". The appropriateness of treating patients with pressure overloading lesions such as aortic stenosis with drugs acting in the renin-angiotensin-aldosterone-system in has been debated. Concerns about the potential risks have prevented the widespread use of ACE-I to treat concomitant hypertension in this context, however evidence in adults suggests these concerns are largely unfounded (Cox et al., 1998; Marquis-Gravel et al., 2016)
9	ACE-I therapy should NOT be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction.	• 84% of the survey participants reported using ACE-I to treat symptomatic and/or asymptomatic patients with single ventricle congenital heart diseases.	The only large randomized controlled trial published testing the effects of ACE-I in children with single ventricle concluded their results did "not support the routine use of enalapril in this population" (Hsu et al., 2010). Other small experimental studies (Kouatli et al., 1997; Lee et al., 2011) also failed to prove any benefit. ISHLT 2014 guideline (Kirk et al., 2014) recommendation in this regard: "ACE-I therapy should not be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction."

Statements		Background	
		Summary of survey results as basis of the topics addressed	Selection and framing of statements
Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy			
10	If beta-blockers are to be introduced for the management of heart failure, patients should also receive an ACE-I concomitantly.	• 55% of the 89 survey participants that reported prescribing drug treatment to patients with DCM that are asymptomatic choose a therapy that includes a beta-blocker; 29% in a two-drug only combination with an ACE • 94% of the participants reported using beta-blockers in symptomatic patients. Approximately half of them introduce ACE-I first ad add beta-blockers in a further step if patients remain symptomatic.	A Cochrane review of 2016 (Alabed et al., 2016)concluded there is not enough evidence to encourage or discourage their use but existing data suggest that children with congestive heart failure might benefit from treatment with beta-blockers. In adults, beta-blockers are recommended in both symptomatic and asymptomatic patients with heart failure with low ejection fraction, always in combination with an ACE-I. However, benefits in asymptomatic patients without a history of myocardial infarction are less clear and recommendations not uniform(McMurray et al., 2012; Yancy et al., 2013). Paediatric guidelines have adopted similar recommendations in the absence of definitive paediatric data (Kantor et al., 2013; Kirk et al., 2014).
11	Beta-blockers should be considered for the management of patients with heart failure in asymptomatic stages.		
12	Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).	• 61% of the participants reported starting the therapy of symptomatic DCM patients with a drug regimen based on an ACE-I and an aldosterone antagonist.	Aldosterone antagonists have proven to have a positive impact in terms of survival and hospitalizations reduction in adults with heart failure when used at low doses (below those prescribed when used with diuretic purposes). ESC guidelines for the management of heart failure in adult patients (McMurray et al., 2012) recommend the use of aldosterone antagonists "for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤ 35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker". No evidence exists in this regard for children, but the Canadian Cardiovascular Society (Kantor et al., 2013)has integrated this recommendation into their paediatric guideline). The ISHLT guideline says, "it is reasonable to consider aldosterone antagonists in children", but is no concrete about timing of introduction.
13	Paediatric validated scores for heart failure severity staging should be connected with pharmacotherapeutic recommendations in further guidelines.	• Only half of the physicians questioned reported making use of clinical scores to evaluate the effectiveness of the therapy.	The grading of heart failure signs and symptoms in children remains challenging. Some scores to grade the severity of heart failure in children have been developed (Ross, 2012) and even though none of them has been validated yet as surrogate clinical endpoints with large number of patients, neurohormonal activation and deteriorating clinical status have been shown to correlate with increasing class (Hsu and Pearson, 2009). However, no standard definitions seem to be routinely applied. ISHLT (Kirk et al., 2014) and Canadian (Kantor et al., 2013) paediatric guidelines on heart failure management apply also self-developed and adult-adapted scales when making recommendations of therapy by heart failure stage.

Appendix M: Emails with questionnaire link and reminders

M.1 Email with individualised questionnaire link Delphi round 1

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

Thank you again for accepting to participate in this Delphi study. As previously discussed, we hereby send you your personal link.

If you agree to participate in the study, please select here
Or copy and paste this address into your browser if selecting above does not work:
[DIRECT_ONLINE_LINK]

If possible, please use **Firefox** or **Google Chrome**.

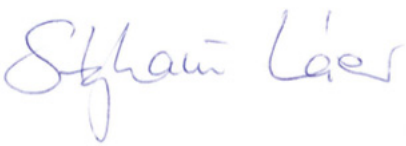
Please, keep in mind that in order to maintain the dynamism of the process, we would like you to submit the filled in questionnaire within one week (until 20th of July).

On the 27th of July at the latest you will receive the second round of the questionnaire as well as feedback from the first round results.

If you have any questions or difficulty with the questionnaire, please contact us at cristina.castro.diez@uni-duesseldorf.de

We thank you in advance for your collaboration and are at your disposal to provide any additional information that you may need.

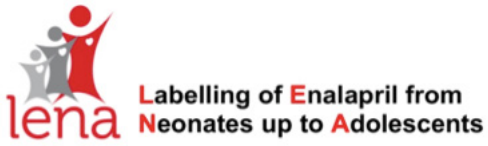
Sincerely,



Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA research assistant
cristina.castro.diez@uni-duesseldorf.de

M.2 Email reminder Delphi round 1



Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

Thank you again for accepting to participate in this Delphi study.

We perfectly understand how busy you are. At the same time, **your participation is extremely important**, as your data will be an essential contribution to making the information collected as valuable as possible.

Therefore **we would greatly appreciate it if you could take 15 minutes to answer the questions and submit the filled in questionnaire before tomorrow**.

If you have any questions or difficulty, please contact us at cristina.castro.diez@uni-duesseldorf.de

If you agree to participate in the study, please select here
Or copy and paste this address into your browser if selecting above does not work:
[DIRECT_ONLINE_LINK]

If possible, please use **Firefox** or **Google Chrome**.

We thank you in advance for your collaboration and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA research assistant
cristina.castro.diez@uni-duesseldorf.de

M.3 Email with individualised questionnaire link Delphi round 2

Labelling of Enalapril from Neonates up to Adolescents

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

Thank you very much for participating in the first round of our Delphi study.

Consensus has already been reached for 7 out of 14 statements.

In the second round you will only find the 7 non-consensus statements.

In the online questionnaire, **feedback from the first round is presented for each statement** with the following structure:

- Frequencies of the answers given by the panel (percentage of experts that selected each answer option).
- Mean score and the 95% confidence interval around it for each of the statements.
- Summary of rationale/comments that were given to the statement.
- Further explanations by the research team.

We would like you to **re-evaluate your level of agreement once again with these 7 statements** in light of the provided feedback. Of course, you can select the same answer as before or change your position, if you consider it now to be more appropriate.

If you agree to participate in the second round of the study, please select here
Or copy and paste this address into your browser if selecting above does not work:
[DIRECT_ONLINE_LINK]

If possible, please use **Firefox** or **Google Chrome**.

Please, keep in mind that in order to maintain the dynamism of the process, we would like you to submit the filled in questionnaire within one week (until 4th of August).

If you have any questions or difficulty with the questionnaire, please contact us at cristina.castro.diez@uni-duesseldorf.de

We thank you in advance for your collaboration and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA research assistant
cristina.castro.diez@uni-duesseldorf.de

M.4 Email reminder Delphi round 2

Dear [[PARTICIPANT_CUSTOM1] [PARTICIPANT_TITLE] [PARTICIPANT_LASTNAME]],

Thank you again for participating in the first round of our Delphi study.

As explained in our last e-mail of the 27th of July, consensus has already been reached for 7 out of 14 statements.

In the second round you will only find the 7 non-consensus statements.

Your participation is extremely important to making the information collected as valuable as possible.

Therefore **we would greatly appreciate it if you could take 15 minutes before Wednesday to re-evaluate your level of agreement with these 7 statements in light of the provided feedback.** Of course, you can select the same answer as before or change your position, if you consider it now to be more appropriate.

If you agree to participate in the second round of the study, please select here
Or copy and paste this address into your browser if selecting above does not work:
[DIRECT_ONLINE_LINK]

If possible, please use **Firefox** or **Google Chrome**.

If you have any questions or difficulty, please contact us at cristina.castro.diez@uni-duesseldorf.de

We thank you in advance for your collaboration and are at your disposal to provide any additional information that you may need.

Sincerely,

Prof. Dr. Stephanie Läer
LENA coordinator
stephanie.laeer@uni-duesseldorf.de

Cristina Castro Díez
LENA research assistant
cristina.castro.diez@uni-duesseldorf.de

Appendix N: Delphi study – Questionnaire[1]

Delphi study on the pharmacotherapeutic management of paediatric heart failure

Angiotensin-converting enzyme inhibitors (ACE-I): Considerations for optimal dosage

1. There is a need for clear monitoring schedules for the early detection of acute kidney injury in paediatric patients on ACE-I therapy.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

2. There is a need for clear blood pressure cut-off points for decision making when up-titrating the dose of ACE-I in paediatric patients.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

[1] Please note that the questionnaire was not distributed to participants in the present format but using web-survey platform EvaSys®

3a. In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

3b. In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

4. If deterioration of the renal function occurred in a patient on ACE-I therapy, concomitant diuretic medication should be readjusted before deciding to down titrate/ stop up-titrating the ACE-I.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

5. If no adverse events occur, ACE-I dose should be increased to the target dose, even if the patient has already experienced improvement with a lower dose.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

6. In order to maximise the accuracy of the ACE-I dose given, the use of different types of formulations for a patient throughout the duration of the treatment should be avoided.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

ACE-I for the management of congenital heart diseases

7. Paediatric patients with <u>asymptomatic</u> mitral or aortic regurgitation benefit from ACE-I therapy.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

8. Paediatric patients with pressure overload lesions should be routinely prescribed ACE-I.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

9. ACE-I therapy should <u>NOT</u> be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy

10. If beta-blockers are to be introduced for the management of heart failure, patients should also receive an ACE-I concomitantly.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

11. Beta-blockers should be considered for the management of patients with heart failure in asymptomatic stages.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

12. Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

13. Paediatric validated scores for heart failure severity staging should be connected with pharmacotherapeutic recommendations in further guidelines.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

Demographic characteristics

14. How many years of experience do you have in the field of paediatric cardiology?

Please select one item.

- ☐ < 1 year
- ☐ 1 to 5 years
- ☐ > 5 to 10 years
- ☐ > 10 years

15. In which type of unit/ centre do you work?

Please select one item.

- ☐ Hospital paediatric cardiology unit
- ☐ Hospital paediatric critical care unit
- ☐ Hospital neonatology unit
- ☐ Hospital clinical pharmacology unit
- ☐ Private practice of paediatric cardiology
- ☐ Other (please specify):

16. In which country do you work?

Please type the name of the country in the box.

Appendix O: Delphi study – Statistical analysis manual

O.1 Table of contents

O.2 Aim of the manual

The manual is intended to provide work description and instructions for the preparation, processing, and analysis of the data that are to be obtained from the Delphi study on the pharmacological management of paediatric heart failure. This study is part of LENA WP12.

O.3 Tasks and responsibilities

Task Name	Responsible	Deadline*	Current status
Identifying study participants and its contact data	Castro	29th June 2015	Done
Developing and designing questionnaire	Castro	29th June 2015	Done
Designing first round questionnaire in web survey tool EvaSys®	Castro/ Makowski	9th July 2015	Done
Preparing manual for statistical analysis	Castro	9th July 2015	Done
Preparing R-Studio® code for analysis of results	Khalil	9th July 2015	Done
Performing the Delphi study first round and collecting its results	Castro	July 2015	Done
Delphi study first round: Extracting data from EvaSys® and preparing Excel® compilation files	Castro/ Makowski	July 2015	Done
Delphi study first round: Encoding of data and preparing ready-to-analyse CSV files	Castro/ Makowski	July 2015	Done
Delphi study first round: Performing statistical analysis of data in R-Studio®	Khalil	July 2015	Done
Preparing feedback and questionnaire for Delphi study second round	Castro/ Makowski	July 2015	Done
Designing second round questionnaire in web survey tool EvaSys®	Castro/ Makowski	July 2015	Done
Performing the Delphi study second round and collecting its results	Castro/ Makowski	July - August 2015	Done
Delphi study second round: Extracting data from EvaSys® and preparing Excel® compilation files	Castro/ Makowski	August – September 2015	Done
Delphi study second round: Encoding of data and preparing ready-to-analyse CSV files	Castro/ Makowski	August – September 2015	Done
Delphi study second round: Performing statistical analysis of data in R-Studio®	Khalil	August – September 2015	Done
Preparing the Delphi study results report to be included in WP12 final report	Castro	October 2016	Done

* Deadline dates are illustrative and might be modified during the course of the study

Tbdn: to be done next; Nys: not yet started; Ip: in process

O.4 Overview of data flow

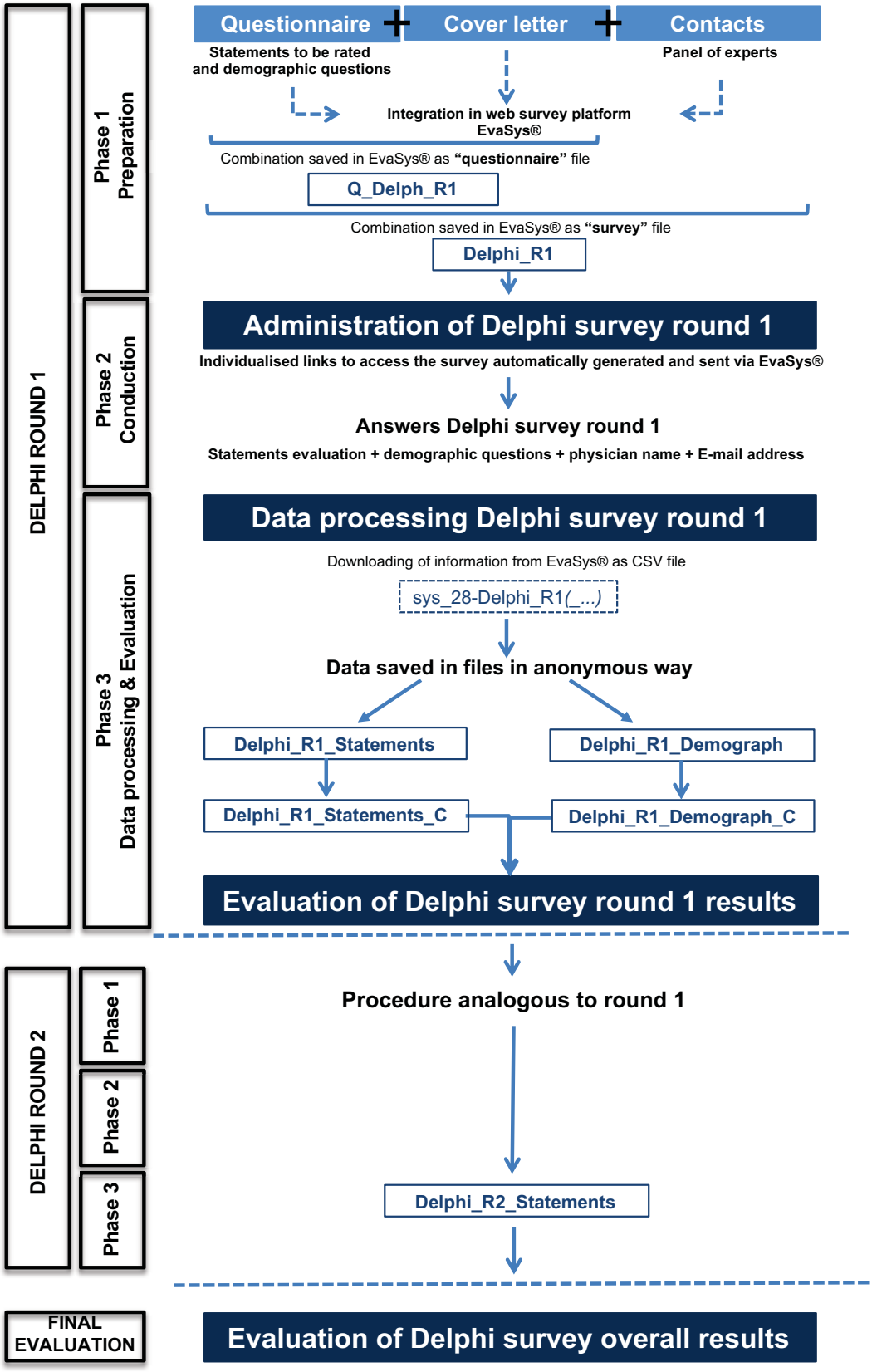


Figure O1. Data flow in WP12 Delphi study

O.4.1 Preparation: Generation of Delphi surveys in web survey tool EvaSys®

In the first round of the study participants will be asked to evaluate their level of agreement with 14 statements and answer 3 demographic questions. In the second round only the statements on which consensus is not achieved in the first round will be presented.

Web-survey platform EvaSys® (version 6.1) will be used. The combination of a questionnaire (containing the statements to be evaluated and the demographic questions, and the cover letter) and a group of participants are required to create a survey in EvaSys®. One different questionnaire will be created for each study round. If, for any reason, different cover letters are necessary to approach different participants, more than a questionnaire (and a survey) per round might be created. Participants' contacts data (physician name and e-mail address) will be entered in EvaSys® under a so-called "Lehrveranstaltung". This can be done via a CSV file or manually. Per each participants group to be entered, a "Lehrveranstaltung" needs to be previously created. EvaSys® will automatically name the later created survey, after the name of the "Lehrveranstaltung" under which the participants are saved. Thus, at least one "Lehrveranstaltung" for each study round will be necessary. An overview of the nomenclature and content of the different surveys, questionnaires and files of contacts is given in **Tables O1**, **O2** and **O3**. If more than a survey per round has to be created, further surveys will be named adding a correlative number (e.g. *Delphi_R1_2, Delphi_R1_3,* etc.). If more than a survey per round has to be created, further contact CSV files will be named adding a correlative number (e.g. Contacts_Dephi_R1_2, Contacts_Dephi_R1_3, etc.).

Table O1. Details of the components of the different versions of the survey saved in EvaSys®

Survey name	Included Questionnaire	Cover letter form	Targeted contact group
Delphi_R1	Q_Delph_R1	English first round	Contacts_Dephi_R1
Delphi_R2	Q_ Delph_R2	English second round	Contacts_Delphi_R2

Table O2. Details of the questionnaires

Questionnaire	Description of questions
Q_Delph_R1	Questionnaire containing the 14 statements to be rated for Delphi study + 3
Q_ Delph_R2	Questionnaire containing only the statements for which no consensus was achieved in round 1, as well as feedback and comments about first round results

Table O3. Details of the imported contact groups

CSV file name	Included contact group
Contacts_Dephi_R1	Experts participating in Delphi study round 1
Contacts_Delphi_R	Experts participating in Delphi study round 2

O.4.2 Conduction

E-mails containing the link to access the Delphi survey will be sent via EvaSys®. A unique link will be automatically generated per study round for each participant. The information collected from the filled-out questionnaires submitted by participants will be automatically stored in EvaSys®.

O.4.3 Data processing and evaluation

Viewing the data stored in EvaSys® is only possible by downloading it, either as a CSV or a PDF file. These files are named automatically by EvaSys® as *sys_28-* followed by the name of the survey they belong to. As agreed in the procedure plan description for the data protection guarantee of this project only files containing Delphi study answers in an anonymous way will be used for the processing and evaluation of the data. Thus, the *sys_28-...* files will only be used with the purpose of creating these anonymised files and deleted directly afterwards. Details are given in section O.5.

O.5 Data processing

The information will be collected and handled according to the procedure plan description for the data protection guarantee of this project (*Verfahrensverzeichnis*), approved by the data protection officer of the Heinrich-Heine University of Düsseldorf by 3rd of June 2015. This procedure follows the

requirements of the North Rhine-Westphalia Data Protection law, in compliance with the EU Data Protection Directive 95/46/EC.

O.5.1 Data extraction and entry

As above explained, information from the answered questionnaires submitted by study participants will be automatically stored in EvaSys®. Files that are to be downloaded from EvaSys® (sys_28-...) will only be used with the purpose of creating anonymised files and deleted directly afterwards. Non-anonymous information will remain stored in EvaSys® platform for 6 months after the study start. As agreed in the procedure plan description for data protection guarantee, throughout this period this non-anonymous data can be consulted when necessary by the investigators team to guarantee the adequate conduction of the Delphi process, but never stored in files out from EvaSys® and/or displayed to third parties. In **Figure O2** the structure that downloaded files with results of the first study round will have is shown. Structure of files containing second round results will be analogous but will not contain the informed consent agreement and the demographic questions (which are only to be asked once) and will only include statements on which consensus is not reached in the first round.

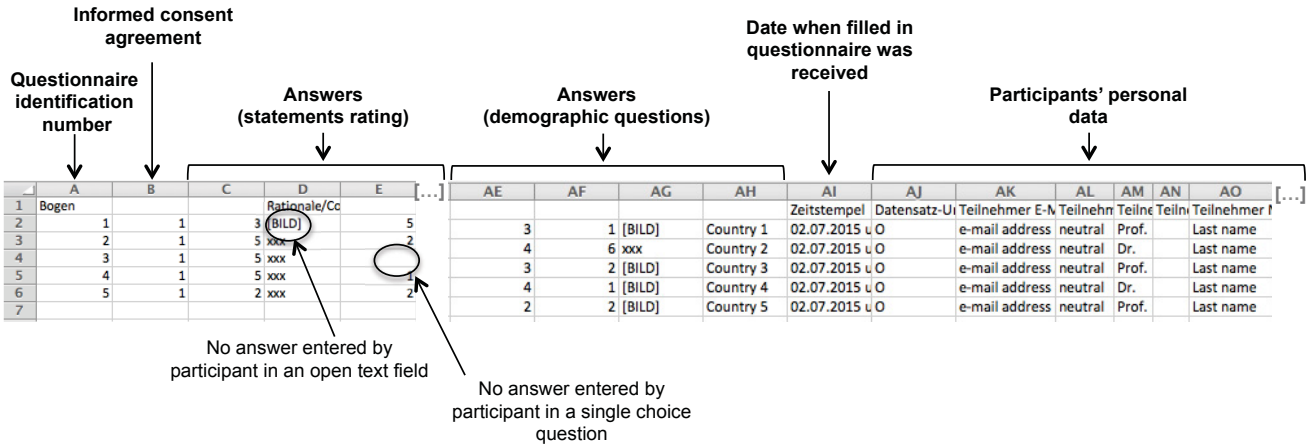


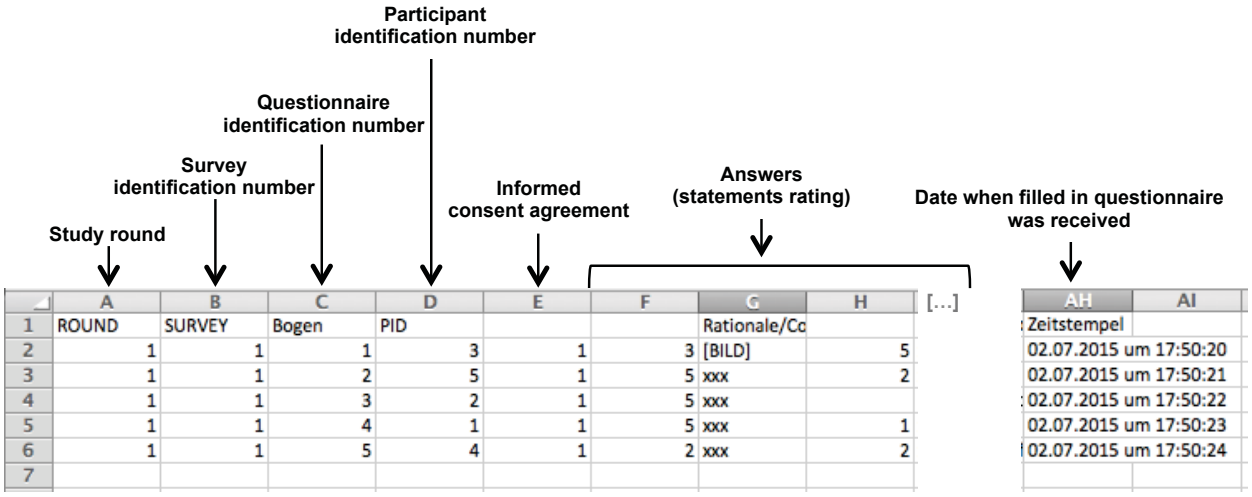
Figure O2. Example CSV file *sys_28-Delphi_R1*

For the creation of the anonymous files, the corresponding Delphi round number, survey identification number (see section O5.2.3) and participant identification number (see section O5.2.4) will be entered in extra columns. Physicians' names and e-mail addresses will be deleted. Furthermore, demographic information asked to participants in round one, will be separated from other answers. Files will be saved with Excel® and CSV format. The files will be named after the survey they are related to, adding to the name the answers they contain and the date (e.g. Delphi_R1_Statements_2015_07_20, Delphi_R1_Demograph_2015_07_20). If more than one survey has to be created in EvaSys® for any of the study rounds, a final compilation file will be created. These files will receive a name analogous to the ones described above but adding a "C" (e.g. Delphi_R1_Statements_C_2015_07_20). After completion of the Delphi process 3 files will contain all the data collected. An overview of the nomenclature and content of each file is given in **Table O4**.

Table O4. Files

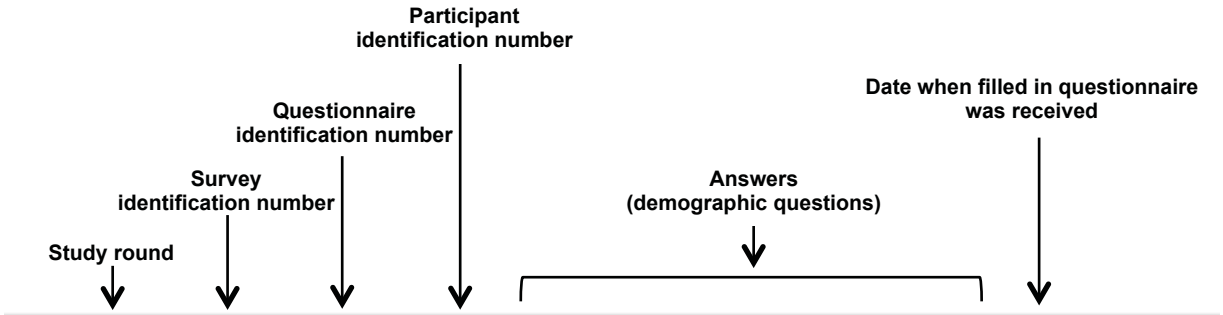
File Name	File Description
Delphi_R1_Statements (or Delphi_R1_Statements_C)	Answers given by participants to questions 1 to 13 (14 statements to be rated) in round 1 together with the informed consent agreement, Delphi round number, survey number, participant identification number, questionnaire reference number and date when questionnaire was received.
Delphi_R1_Demograph (or Delphi_R1_Demograph_C)	Answers given by participants to questions 14 to 16 (questions on demographic characteristics) together with Delphi round number, survey number, participant identification number, questionnaire reference number and date when questionnaire was received.
Delphi_R2_Statements (or Delphi_R2_Statements_C)	Answers given by participants to the questions presented for discussion in second study round together with Delphi round number, survey number, participant identification number, questionnaire reference number and date when questionnaire was received.

In **Figures O3** and **O4** the structure the first sheet of these files will have is shown. The second sheet will be a copy of the first one in which the pre-specified variables headings (see **Table O5**) will be entered in the first row. This second sheet will be further saved in CSV form, resulting in the ready-to-analyse file required for R-Studio®. The CSV files will receive the same name of the Excel® file they belong to. The correct data extraction, entry and encoding will be verified. The procedures will be conducted by 2 researchers independently with the help of a checklist (**Appendices O-A** and **O-B**) and results will be checked for consistency.



	A	B	C	D	E	F	G	H	AH	AI
1	ROUND	SURVEY	Bogen	PID			Rationale/Co		Zeitstempel	
2	1	1	1	3	1	3	[BILD]	5	02.07.2015 um 17:50:20	
3	1	1	2	5	1	5	xxx	2	02.07.2015 um 17:50:21	
4	1	1	3	2	1	5	xxx		02.07.2015 um 17:50:22	
5	1	1	4	1	1	5	xxx	1	02.07.2015 um 17:50:23	
6	1	1	5	4	1	2	xxx	2	02.07.2015 um 17:50:24	
7										

Figure O3. Example Excel® file Delphi_R1_Statements



	A	B	C	D	E	F	G	H	I	J
1	ROUND	SURVEY	Bogen	PID					Zeitstempel	
2	1	1	1	3	3	1	[BILD]	Country 1	02.07.2015 um 17:50:20	
3	1	1	2	5	4	6	XXX	Country 2	02.07.2015 um 17:50:21	
4	1	1	3	2	3	2	[BILD]	Country 3	02.07.2015 um 17:50:22	
5	1	1	4	1	4	1	[BILD]	Country 4	02.07.2015 um 17:50:23	
6	1	1	5	4	2	2	[BILD]	Country 5	02.07.2015 um 17:50:24	
7										

Figure O4. Example Excel® file Delphi_R1_Demograph*

*At the latest 6 months after study completion columns SURVEY, Bogen (ID, see section 6.2), PID and ZEITSTEMPEL will be deleted from files containing answers to demographic questions. This will allow the final anonymisation of the data.

O.5.2 Nomenclature

O.5.2.1 Questionnaire identification number (ID)

Each of the filled-out questionnaires submitted by study participants will receive an identification number when stored in EvaSys®. This number will be assigned automatically. Within each of the created surveys, the first returned questionnaire will receive the identification number 1 and correlative numbers will be assigned to further questionnaires following a chronological order. Thus, if more than a survey needs to be created in each study round, different answered questionnaires will receive a same ID. Similarly, a same ID will be assigned to completed questionnaires form the first and second study round. To allow the correct identification of each questionnaire, as above explained, extra columns containing study round number and survey number will be added in the downloaded files before saving the information.

O.5.2.2 Study round number (ROUND)

Questionnaires corresponding to study round 1 will be given a "1" and questionnaires corresponding to study round 2 a "2".

O.5.2.3 Survey identification number (SURVEY)

Within each study round questionnaires belonging to the first of the created surveys (e.g. Delphi_R1 for first study round) will be assigned the number 1 and correlative numbers will be given to questionnaire from further surveys (e.g. Delphi_R1_2 → number 2).

O.5.2.4 Participant identification number (PID)

Prior to the beginning of the study, a unique identification number will be assigned to each of the study participants. This code will be entered before making the data anonymous. The PID will allow the identification of each participant throughout the 2 study rounds. The file containing study

participant's names with the corresponding PID will be deleted at the latest 6 months after study completion.

O.5.2.5 Data encoding system

The first-round questionnaire will be formed by 17 single choice closed questions (SCQ) and 1 open text question (OTQ). The first single choice question (question 0) will be the informed consent, which is to be agreed electronically by study participants. Fourteen statements to be rated and 3 demographic questions will follow. Each statement is to be rated by using a SCQ in the form of a 5-point Likert scale. An open text field where comments to the answers given can be entered will accompany. Two of the demographic questions are SCQ (14 and 15), one of them including an "other" option. If this was selected, an open text field where participants can enter further details will display. The last of the demographic questions is OTQ type. The questionnaire to be administered in the second round of the study will contain only those statements on which consensus could not be reached in the first study round. Each statement will be presented again with a SCQ and an open text field.

Information coming from SCQ is collected by EvaSys® in encoded form (see **Table O5**). A numeric code is automatically given to each response option. Information coming from OTQ is stored in text form. The variables will be named starting always with a "q" followed by the number of the question they belong to. Variables names are also detailed in Excel® file Coding_system_of_delphi_round_1. For round 2 an analogous file will be prepared.

Table O5. Encoding system

Ques.	Type of question	Variable name Excel®	Value	Label
		ROUND	1	Delphi study round 1
			2	Delphi study round 2
-	-	SURVEY	Number 1 to …	-
-	-	ID	Number 1 to ...	-
-	-	PID	Number 1 to ...	-
0	SCQ	CONSENT	1	Selected
			0	Not selected
1	SCQ	q1_MONIT_AKI	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q1_COMMENT	Free text*	-
2	SCQ	q2_MONIT_BP	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q2_COMMENT	Free text*	-
3a	SCQ	q3a_UT_INTERVAL	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q3a_COMMENT	Free text*	-
3b	SCQ	q3b_UT_DOUBLE	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree

Ques.	Type of question	Variable name Excel®	Value	Label
			5	Strongly agree
		q3b_COMMENT	Free text*	-
4	SCQ	q4_DIURETICS	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q4_COMMENT	Free text*	-
5	SCQ	q5_TARGET	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q5_COMMENT	Free text*	-
6	SCQ	q6_FORMUL	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q6_COMMENT	Free text*	-
7	SCQ	q7_VR	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q7_COMMENT	Free text*	-
8	SCQ	q8_P_OVERLOAD	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree

Ques.	Type of question	Variable name Excel®	Value	Label
			5	Strongly agree
		q8_COMMENT	Free text*	-
9	SCQ	q9_SV	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q9_COMMENT	Free text*	-
10	SCQ	q10_BB_ACEI	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q10_COMMENT	Free text*	-
11	SCQ	q11_BB_ASYMP	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q11_COMMENT	Free text*	-
12	SCQ	q12_AA	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree
			5	Strongly agree
		q12_COMMENT	Free text*	-
13	SCQ	q13_SCORES	1	Strongly disagree
			2	Disagree
			3	Neither agree, nor disagree
			4	Agree

Ques.	Type of question	Variable name Excel®	Value	Label
			5	Strongly agree
		q13_COMMENT	Free text*	-
14	SCQ	q14_YEARS_EXP	1	< 1 year
			2	1 to 5 years
			3	> 5 to10 years
			4	> 10 years
15	SCQ	q15_UNIT	1	Hospital paediatric cardiology unit
			2	Hospital paediatric critical care unit
			3	Hospital neonatology unit
			4	Hospital clinical pharmacology unit
			5	Private practice of paediatric cardiology
			6	Other
		q15_UNIT_FTXT	Free text*	
16	OTQ	q16_COUNTRY	Free text*	
-	-	ZEITSTEMPEL	Free text*	-

O.6 Data analysis

O.6.1 Used software tools

The statistical analysis of the data will be performed using R-Studio® version 099.465 and R® v.3.2.3.

O.6.2 Parameters of interest

For SCQ the absolute and relative frequency with which each response option is selected will be presented. The level of consensus among experts on each of the 14 statements to be judged will be studied. The mean 5-point Likert-scale score and the corresponding 95% confidence interval (CI) will be calculated. Consensus will be defined as follows (Fick et al., 2003; Holt et al., 2010; Medrano López et al., 2010):

- Upper bounder of CI < 3: consensus exist among experts that a statement is false.
- Lower bounder of CI > 3: consensus exist among experts that a statement is true.
- CI includes the 3: no consensus exists among experts on whether a statement is or not true.

Statements were no consensus is reached after second study round will be descriptively analysed. The stability of responses among first and second study round, the existence of bimodal distributions and the reasons leading to no-consensus (most participants "neither agreeing nor disagreeing" or diversity of opinions) will be investigated. For this purpose, results of both study rounds (absolute frequency of the different answer options) will be represented as bar plots. Response rate for each Delphi round will also be calculated.

O.6.3 Calculations of the statistical parameters

Incomplete questionnaires will be taken into consideration. If a participant submits a filled in questionnaire only for the first study round, this will be taken into consideration. Within each study round calculations will be made considering as total number of subjects the ones having submitted a questionnaire, either fully or partially completed. Percentages will be given one decimal point. Mean values of Likert score rating will be given with 2 decimal points. Parameters mentioned in section O.6.2 will be calculated as follows:

- Mean

$$\overline{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

- Median

If number of values odd $M_e = x_{(n+1)/2}$

If number of values even $M_e = (x_{\frac{n}{2}} + x_{\frac{n}{2}+1})/2$

- Standard deviation

$$s = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

- 95% confidence interval (CI)

$95\%\ \mathrm{CI} = \bar{x} \pm 1{,}96 \times \frac{S}{\sqrt{n}}$

- Response rate

Response rate will be calculated for each study round as the number of subjects that returned a completed or partially completed questionnaire divided by the number of subjects that were sent the questionnaire

O.6.4 Results reporting

Details about how the results will be reported are given below.

Rating of statements: Questions 1 to 13

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %) • Mean and median
Inferential statistics	• Confidence interval of the mean
Presentation of results	• Table (please see example **Tables O6**, **O7** and **O8**) • Bar plot with frequency of selection of each answer option (for statement not reaching consensus after round 2 results of both rounds will be presented together in a figure for comparison)

Table O6. Example table for the presentation of distribution of answers

There is a need for clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.		
	n/ total	**(%)**
Strongly disagree		
Disagree		
Neither agree nor disagree		
Agree		
Strongly agree		
Missing answers		

Table O7. Example table for the presentation of rationale/comments given by participants to each statement

List of comments		**Score selected by the participant**
1	…	…
…	…	…

Table O8. Example table for the presentation of results of consensus evaluation

Statement	**Statement evaluation on the 5-point Likert scale**		
	Median	**Mean**	**95% CI**
There is a need of clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.			

General results of the Delphi procedure

Descriptive statistics	• Relative frequency of consensus process (statements accepted, rejected, undecided after each round)
Inferential statistics	-
Presentation of results	•Table (please see example **Table O9**)

Table O9. Example table for the presentation of summarised results of the Delphi procedure

		Statements		
	Presented	**Reaching consensus**		**Not reaching consensus**
		Accepted	**Rejected**	
		n/total	n/total	n/total
Delphi round 1 (nº of panellists)				
Delphi round 2 (nº of panellists)				
Total				

Demographic questions

Question 14: How many years of experience do you have in the field of paediatric cardiology?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table (please see example **Table O10**) • Pie chart

Table O10. Example table for the presentation of results of question 14 (Years of experience in the field of paediatric cardiology)

Years		
	n/total	**%**
<1 year		
1-5 years		
5-10 years		
> 10 years		

Question 15: In which type of unit/ centre do you work?

Type of question	SCQ
Descriptive statistics	• Absolute and relative frequency (number and %)
Presentation of results	• Table (please see example **Table O11**) • Pie chart

Table O11. Example table for the presentation of results of question 15 (Type of unit where survey participants develop their professional activity)

Type of unit		
	n/total	**%**
Hospital paediatric cardiology unit		
Hospital paediatric critical care unit		
Hospital neonatology unit		
Hospital clinical pharmacology unit		
Private practice of paediatric cardiology		
Other		

Question 16: In which country are you working?

Type of question	OTQ
Descriptive statistics	• Response rate will be calculated after each round by dividing the number of totally + partially completed questionnaires by the total number of eligible invited clinicians.
Presentation of results	• Table (please see example table O12) • Pie chart

Table O12. Example table for the presentation of results of question 16 (Delphi study participation/experts by country)

Country		
	n/total	**%**

O.7 Appendix O-A: Checklist data extraction and encoding Delphi round 1

(Work instructions during creation of files
Delphi_R1_Statements/ Delphi_R1_C_Statements
and Delphi_R1_Demograph/ Delphi_R1_C_Demograph)

Check if done

37. CSV file sys_28-Delphi_R1*(_…)* downloaded. ☐
38. Column A with Delphi study round number entered in file sys_28-Delphi_R1*(_…)*. ☐
39. Column B with survey number entered in file sys_28-Delphi_R1*(_…)*. ☐
40. Column D with participant identification number entered in file sys_28-Delphi_R1*(_…)*. ☐
41. Expert's personal data (columns AM to AV) deleted from file sys_28-Delphi_R1*(_…)*. ☐
42. Excel® file with the name Delphi_R1_Statements_*year_month_day* (or Delphi_R1_1_Statements_*year_month_day*, if more than a survey for study round 1 exists) created. ☐
43. Excel® file with the name Delphi_R1_Demograph_*year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day*, if more than a survey for study round 1 exists) created. ☐
44. Columns containing answers to demographic questions (columns AH to AK) deleted from file Delphi_R1_Statements_*year_month_day* (or Delphi_R1_1_Statements_ *year_month_day*) and file is saved. ☐
45. Columns containing answers to statements and informed consent (columns E to AG) are deleted from file Delphi_R1_Demograph_*year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day)* and file is saved. ☐
46. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R1_2_Statements_ ☐

year_month_day , Delphi_R1_2_Demograph_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed.

47. If more than a survey was created for the first round study, all data of Delphi_R1_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day* ☐
48. Excel® sheet of file Delphi_R1_Statements_*year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied.* ☐
49. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Statements_ *year_month_day* (or Delphi_R1_Statements_C_ *year_month_day).* ☐
50. Variables headings correspond with the entered data (number of columns is the same, A to AH). ☐
51. If more than a survey was created for the first round study, all data of Delphi_R1_Demograph (Delphi_R1_Demograph, Delphi_R1_2_Demograph,…) compiled in file Delphi_R1_Demograph_C_ *year_month_day*. ☐
52. Excel® sheet of file Delphi_R1_Demograph_*year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day) copied.* ☐
53. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Demograph_ *year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day).* ☐
54. Variables headings correspond with the entered data (number of columns is the same, A to I). ☐
55. Files sys_28-Delphi_R1*(_…)* deleted. ☐
56. CSV file Delphi_R1_Statements (or Delphi_R1_C_Statements) created. ☐
57. CSV file Delphi_R1_Demograph (or Delphi_R1_C_Demograph) created. ☐

Further comments:

The content listed above has been checked and is correct

_____

Name, Date, Signature

O.8 Appendix O-B: Checklist data extraction and encoding Delphi round 2

(Work instructions during creation of files Delphi_R2_Statements/ Delphi_R2_C_Statements)

Check if done

1. CSV file sys_28-Delphi_R2*(_…)* downloaded. ☐
2. Column A with Delphi study round number entered in file sys_28-Delphi_R2*(_…)*. ☐
3. Column B with survey number entered in file sys_28-Delphi_R2*(_…)*. ☐
4. Column D with participant identification number entered in file sys_28-Delphi_R2*(_…)*. ☐
5. Expert's personal data (columns _ to _) deleted from file sys_28-Delphi_R2*(_…)*. ☐
6. Excel® file with the name Delphi_R2_Statements*_year_month_day* (or Delphi_R2_1_Statements*_year_month_day*, if more than a survey for study round 2 exists) created. ☐
7. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R2_2_Statements_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed. ☐
8. If more than a survey was created for the first round study, all data of Delphi_R2_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day.* ☐
9. Excel® sheet of file Delphi_R2_Statements*_year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied.* ☐
10. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R2_Statements_ *year_month_day* (or Delphi_R2_Statements_C_ *year_month_day)* ☐
11. Variables headings correspond with the entered data (number of columns is the same, _ to _). ☐

12. Files sys_28-Delphi_R2*(_…)* deleted. ☐

13. CSV file Delphi_R2_Statements (or Delphi_R2_C_Statements) created. ☐

Further comments:

The content listed above has been checked and is correct

Name, Date, Signature

Appendix P: Delphi study – Signed checklists

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 1 of 3**

(Work instructions during creation of files Delphi_R1_Statements/ Delphi_R1_C_Statements and Delphi_R1_Demograph/ Delphi_R1_C_Demograph)

	Check if done
1. CSV file sys_28-Delphi_R1*(_…)* downloaded.	✔ ✔ ✔
2. Column A with Delphi study round number entered in file sys_28-Delphi_R1*(_…)*.	✔ ✔ ✔
3. Column B with survey number entered in file sys_28-Delphi_R1*(_…)*.	✔ ✔ ✔
4. Column D with participant identification number entered in file sys_28-Delphi_R1*(_…)*.	✔ ✔ ✔
5. Expert's personal data (columns AM to AV) deleted from file sys_28-Delphi_R1*(_…)*.	✔ ✔ ✔
6. Excel® file with the name Delphi_R1_Statements*_year_month_day* (or Delphi_R1_1_Statements*_year_month_day*, if more than a survey for study round 1 exists) created.	✔ ✔ ✔
7. Excel® file with the name Delphi_R1_Demograph*_year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day*, if more than a survey for study round 1 exists) created.	✔ ✔ ✔
8. Columns containing answers to demographic questions (columns AH to AK) deleted from file Delphi_R1_Statements*_year_month_day* (or Delphi_R1_1_Statements_ *year_month_day*) and file is saved.	✔ ✔ ✔
9. Columns containing answers to statements and informed consent (columns E to AG) are deleted from file Delphi_R1_Demograph*_year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day)* and file is saved.	✔ ✔ ✔
10. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R1_2_Statements_ *year_month_day* , Delphi_R1_2_Demograph_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed.	✔

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 2 of 3**

11.	If more than a survey was created for the first round study, all data of Delphi_R1_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day*		✔
12.	Excel® sheet of file Delphi_R1_Statements_*year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied.*		✔
13.	Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Statements_ *year_month_day* (or Delphi_R1_Statements_C_ *year_month_day).*		✔
14.	Variables headings correspond with the entered data (number of columns is the same, A to AH).		✔
15.	If more than a survey was created for the first round study, all data of Delphi_R1_Demograph (Delphi_R1_Demograph, Delphi_R1_2_Demograph,…) compiled in file Delphi_R1_Demograph_C_ *year_month_day*.		✔
16.	Excel® sheet of file Delphi_R1_Demograph_*year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day) copied.*		✔
17.	Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Demograph_ *year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day).*		✔
18.	Variables headings correspond with the entered data (number of columns is the same, A to I).		✔
19.	Files sys_28-Delphi_R1*(_…)* deleted.	✔ ✔	✔
20.	CSV file Delphi_R1_Statements (or Delphi_R1_C_Statements) created.		✔
21.	CSV file Delphi_R1_Demograph (or Delphi_R1_C_Demograph) created.		✔

Further comments:
One participant did not use EvaSys to answer the questionnaire, but a PDF copy he requested. He did give informed consent and filled in demographic information via EvaSys. Questionnaire data were manually entered in the compilation Excel file

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 3 of 3**

The content listed above has been checked and is correct

Name, Date, Signature

	Statistical analysis manual for LENA WP12 Delphi study	
	Checklist data extraction and encoding	**Page 1 of 2**

(Work instructions during creation of files Delphi_R2_Statements/ Delphi_R2_C_Statements)

	Check if done
1. CSV file sys_28-Delphi_R2*(_…)* downloaded.	✔
2. Column A with Delphi study round number entered in file sys_28-Delphi_R2*(_…)*.	✔
3. Column B with survey number entered in file sys_28-Delphi_R2*(_…)*.	✔
4. Column D with participant identification number entered in file sys_28-Delphi_R2*(_…)*.	✔
5. Expert's personal data (columns _ to _) deleted from file sys_28-Delphi_R2*(_…)*.	✔
6. Excel® file with the name Delphi_R2_Statements*_year_month_day* (or Delphi_R2_1_Statements*_year_month_day*, if more than a survey for study round 2 exists) created.	✔
7. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R2_2_Statements_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed.	✔
8. If more than a survey was created for the first round study, all data of Delphi_R2_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day*.	✔
9. Excel® sheet of file Delphi_R2_Statements*_year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied*.	✔
10. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R2_Statements_ *year_month_day* (or Delphi_R2_Statements_C_ *year_month_day)*	✔

	Statistical analysis manual for LENA WP12 Delphi study	
	Checklist data extraction and encoding	**Page 2 of 2**

11. Variables headings correspond with the entered data (number of columns is the same, _ to _). ✔

12. Files sys_28-Delphi_R2(_…) deleted. ✔

13. CSV file Delphi_R2_Statements (or Delphi_R2_C_Statements) created. ✔

Further comments:
One participant did not use EvaSys to answer the questionnaire, but a PDF copy he requested. Data were manually entered in the compilation Excel file.

The content listed above has been checked and is correct

Cristina Castro Diez 03.10.2015

Name, Date, Signature

lena	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 1 of 3**

(Work instructions during creation of files Delphi_R1_Statements/ Delphi_R1_C_Statements and Delphi_R1_Demograph/ Delphi_R1_C_Demograph)

	Check if done
1. CSV file sys_28-Delphi_R1*(_…)* downloaded.	☑ ☑ ☑
2. Column A with Delphi study round number entered in file sys_28-Delphi_R1*(_…)*.	☑ ☑ ☑
3. Column B with survey number entered in file sys_28-Delphi_R1*(_…)*.	☑ ☑ ☑
4. Column D with participant identification number entered in file sys_28-Delphi_R1*(_…)*.y	☑ ☑ ☑
5. Expert's personal data (columns AM to AV) deleted from file sys_28-Delphi_R1*(_…)*.	☑ ☑ ☑
6. Excel® file with the name Delphi_R1_Statements*_year_month_day* (or Delphi_R1_1_Statements*_year_month_day*, if more than a survey for study round 1 exists) created.	☑ ☑ ☑
7. Excel® file with the name Delphi_R1_Demograph*_year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day*, if more than a survey for study round 1 exists) created.	☑ ☑ ☑
8. Columns containing answers to demographic questions (columns AH to AK) deleted from file Delphi_R1_Statements*_year_month_day* (or Delphi_R1_1_Statements_ *year_month_day*) and file is saved.	☑ ☑ ☑
9. Columns containing answers to statements and informed consent (columns E to AG) are deleted from file Delphi_R1_Demograph*_year_month_day* (or Delphi_R1_1_Demograph_ *year_month_day)* and file is saved.	☑ ☑ ☑
10. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R1_2_Statements_ *year_month_day* , Delphi_R1_2_Demograph_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed.	☑

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 2 of 3**

11. If more than a survey was created for the first round study, all data of Delphi_R1_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day* ☑
12. Excel® sheet of file Delphi_R1_Statements_*year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied.* ☑
13. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Statements_ *year_month_day* (or Delphi_R1_Statements_C_ *year_month_day).* ☑
14. Variables headings correspond with the entered data (number of columns is the same, A to AH). ☑
15. If more than a survey was created for the first round study, all data of Delphi_R1_Demograph (Delphi_R1_Demograph, Delphi_R1_2_Demograph,…) compiled in file Delphi_R1_Demograph_C_ *year_month_day.* ☑
16. Excel® sheet of file Delphi_R1_Demograph_*year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day) copied.* ☑
17. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R1_Demograph_ *year_month_day* (or Delphi_R1_Demograph_C_ *year_month_day).* ☑
18. Variables headings correspond with the entered data (number of columns is the same, A to I). ☑
19. Files sys_28-Delphi_R1*(_…)* deleted. ☑ ☑ ☑
20. CSV file Delphi_R1_Statements (or Delphi_R1_C_Statements) created. ☑
21. CSV file Delphi_R1_Demograph (or Delphi_R1_C_Demograph) created. ☑

Further comments:

One participant gave his consent and demographic answers via EvaSys and evaluated the statements via ~~the~~ PDF-file. This answers were transferred manually after step 6 is repeated for the different surveys.

	Statistical analysis manual for LENA WP12	
Affected WP: WP 12	**Checklist data extraction and encoding**	**Page 3 of 3**

The content listed above has been checked and is correct

Nina Mahowald, 19.4.16, Mahowald

Name, Date, Signature

lena	Statistical analysis manual for LENA WP12 Delphi study	
	Checklist data extraction and encoding	**Page 1 of 2**

(Work instructions during creation of files Delphi_R2_Statements/ Delphi_R2_C_Statements)

	Check if done
1. CSV file sys_28-Delphi_R2(_…) downloaded.	☑
2. Column A with Delphi study round number entered in file sys_28-Delphi_R2(_…).	☑
3. Column B with survey number entered in file sys_28-Delphi_R2(_…).	☑
4. Column D with participant identification number entered in file sys_28-Delphi_R2(_…).	☑
5. Expert's personal data (columns _ to _) deleted from file sys_28-Delphi_R2(_…).	☑
6. Excel® file with the name Delphi_R2_Statements_*year_month_day* (or Delphi_R2_1_Statements_*year_month_day*, if more than a survey for study round 2 exists) created.	☑
7. If more than a survey exists in EvaSys® for study round 1 steps 1 to 9 are done for all of them naming them as corresponds (e.g. Delphi_R2_2_Statements_ *year_month_day*) adding extra boxes to enter the corresponding checks as needed.	n.a.
8. If more than a survey was created for the first round study, all data of Delphi_R2_Statements files (Delphi_R1_1_Statements, Delphi_R1_2_Statements,…) compiled in file Delphi_R1_Statements_C_ *year_month_day.*	☑
9. Excel® sheet of file Delphi_R2_Statements_*year_month_day* (or Delphi_R1_Statements_C_ *year_month_day) copied.*	☑
10. Pre-specified variables headings entered in the first row of the second sheet of Delphi_R2_Statements_ *year_month_day* (or Delphi_R2_Statements_C_ *year_month_day)*	☑

	Statistical analysis manual for LENA WP12 Delphi study	
	Checklist data extraction and encoding	**Page 2 of 2**

11. Variables headings correspond with the entered data (number of columns is the same, A to S). ☑

12. Files sys_28-Delphi_R2(_…) deleted. ☑

13. CSV file Delphi_R2_Statements (or Delphi_R2_C_Statements) created. ☑

Further comments:

One participant answered the survey via PDF. Data were manually entered in Excel file with the same structure as the downloaded data from EvaSys. Personal data and "Zeitstempel" were not entered. Thus, step 7 is not applicable. In step 8 both files were combined.

The content listed above has been checked and is correct

Nina Makowski, 23.04.16 NMakowski

Name, Date, Signature

Appendix Q: Delphi study – Data protection procedure plan description

Verfahrensbeschreibung zum Forschungsprojekt:

"Analysing the standard of care of paediatric heart failure across Europe through a Delphi process"

Zur Dokumentation beim behördliche Datenschutzbeauftragten nach § 8 Datenschutzgesetzt Nordrhein-Westfalen vom 2000

Verfahrensbezeichnung:

"Analysing the standard of care of paediatric heart failure across Europe through a Delphi process"

1. Name und Anschrift der datenverarbeitenden Stelle (§ 3 Abs. 3 DSG NRW, § 2 Abs. 2 DSG NRW)

1.1 Name und Anschrift

Name:	Heinrich-Heine-Universität, Institut für Klinische Pharmazie und Pharmakotherapie
Straße:	Universitätstrasse 1
Gebäude:	Gebäude 26.22, Ebene 02, Raum 22-24
PLZ:	40225
Ort:	Düsseldorf
Telefon:	0211-8112531
Fax:	0211-8110741
E-Mail:	cristina.castro.diez@uni-duesseldorf.de

1.2 Organizationskennziffer

Dezernat:	Gebäude 26.22, Ebene 02, Raum 22-24
Institut:	Institut für Klinische Pharmazie und Pharmakotherapie

1.3 Erstellerin des Verfahrensverzeichnisses

Cristina Castro Díez angeordnet durch Leiterin Prof. Stephanie Läer.

1.4 Findet Auftragsdatenverarbeitung gem. § 11 DSG NRW statt?

Ja

1.5 Angaben zur Auftragsdatenverarbeitung

Name und Anschrift

Name:	Electric Paper Evaluationssysteme GmbH (EvaSys®)
Straße:	Konrad-Zuse-Allee 13
PLZ:	21337
Ort:	Lüneburg, Deutschland
Telefon:	+49 4131 7360 0 / +49 4131 7360 50
Fax:	+49 4131 7360 60
E-Mail:	info@evasys.de

Daten die technisch gespeichert werden

Namensangaben, Kommunikationsdaten, Berufsdaten (Arbeitsstätte, Stadt, Land, Jahre an Berufserfahrung in der Behandlung von Kindern mit Herzinsuffizienz) und Meinung zu verschiedenen Aspekten der Arzneimitteltherapie von pädiatrischen Patienten mit Herzinsuffizienz

Bearbeitungsvorgänge die durchgeführt werden

Erhebung, Speicherung, Analyse

2. Bezeichnung, Zweckbestimmung und Rechtsgrundlage der Datenverarbeitung

2.1 Bezeichnung des Verfahrens

Verarbeitung von dem durch die europaweite Delphi-Befragung über die Arzneimitteltherapie von pädiatrischen Patienten mit Herzinsuffizienz erhobene Daten des Institutes für Klinische Pharmazie und Pharmakotherapie der Universität Düsseldorf. Abkürzung: Delphi-Befragung Datenverarbeitung

Es bestehen keine Verknüpfungen zu anderen Verfahrensdataien.

2.2 Zweckbestimmung

Im Rahmen des Projektes werden vor der Befragung Namensangaben (Anrede, Vorname, Nachname)

sowie Kommunikationsdaten (Telefonnummer, E-Mail) und Berufsdaten (Arbeitsstätte, Stadt, Land) erhoben. Durch die Umfrage werden Berufsdaten (Arbeitsstätte, Stadt, Land, Jahre an Berufserfahrung in der Behandlung von Kindern mit Herzinsuffizienz) und die Meinung zu verschiedenen Aspekten der Arzneimitteltherapie von pädiatrischen Patienten mit Herzinsuffizienz erhoben.

Die durch diesen Prozess des Konsensusbildung erhobenen Daten werden benutz um umstrittene Aspekten der Verschreibung von Arzneimitteln für die Behandlung von Kindern mit Herzinsuffizienz in Europa zu klären, sowie um die Aufmerksamkeit auf diese Themen zu lenken.

1. Namensangaben werden erhoben um die Ärzte an der Teilnahme in der Umfrage einladen zu können. Gegebenenfalls, und nur wenn die Teilnehmer schriftlich einwilligen sollten, werden später die Namensangaben mit den Ergebnissen veröffentlicht. Dies würde ohne Zuordnung zu den einzelnen Antworten erfolgen. Ziel diese Veröffentlichung wäre, die Ergebnisse der Befragung in Kontext zu setzen, indem bekannt gemacht wird, welche Experten diese Meinungen erzeugt haben.

2. Kommunikationsdaten werden erhoben um die Ärzte an der Teilnahme in der Umfrage einladen, zu können sowie um die entsprechende Diskussion/ Rückkopplung der Ergebnisse durchführen zu können.

3. Berufsdaten werden erhoben um die Teilnehmer Gruppe zu charakterisieren. Gegebenenfalls, und nur wenn die Teilnehmern schriftlich einwilligen sollten, werden später die Berufsdaten mit den Ergebnissen veröffentlicht. Das würde ohne Zuordnung zu den einzelnen Antworten erfolgen. Ziel diese Veröffentlichung wäre, die Ergebnisse der Befragung in Kontext zu setzen, indem bekannt gemacht wird, was für Experten diese Meinungen erzeugt haben.

4. Meinungen zur Arzneimitteltherapie von pädiatrischen Patienten mit Herzinsuffizienz

werden erhoben, um umstrittene Aspekten zu klären, sowie um die Aufmerksamkeit auf diese Themen zu lenken.

2.3 Rechtsgrundlage der Datenverarbeitung

Die Rechtsgrundlage wird durch die freiwillige, informierte Einwilligung der Studienteilnehmer nach § 28 Absatz 2 gewährleistet.

Die personenbezogenen erhobenen Daten mit Zuordnung zu den einzelnen Antworten, werden nur während der Dauer der Umfrage (4 Monaten) behalten. Die Antworten werden für die Analyse von den personenbezogenen Daten getrennt und nach der genannten Zeit anonymisiert. Die nicht-anonymisierte erste Datenverarbeitung ist für diese Studie am Besten geeignet. Dadurch wird die Rückkopplung und die Diskussion während der Durchführung der Befragung ermöglicht.

Diese Vorgehensweise kann als sicher gehalten werden, da die Schutzwürdigkeit der Daten aus folgenden Gründen als gering beurteilt werden kann:

Das Verstößen gegen der Sicherheit der personenbezogene gespeicherten Daten kaum gesetzliche oder moralische Konsequenzen für die betroffenen haben würden.

Eine Beeinträchtigung des Informationellen Selbstbestimmungsrecht durch den einzelnen als tolerable bezeichnet werden kann.

Eine Beeinträchtigung der persönlichen Unversehrtheit nicht möglich scheint.

Um die Verweigerungsrate zu vermindern, und nach die unter §4 Abs. 1 der DSG NRW berücksichtigte Umstände, wird die Einwilligung elektronisch erklärt. Auf Grund der Schutzwürdigkeit der verarbeitende Daten, kann diese Vorgehensweise für ausreichend gehalten werden.

Sollten die Studienteilnehmer durch die obengenannte Einwilligung zustimmen, könnten bei der Studienergebnisse Veröffentlichung, die Namen und Berufsdaten den Teilnehmer bekannt gemacht

werden. Das würde ohne Zuordnung zu den einzelnen gegeben Antworten erfolgen.

2.4 Werden automatisierte Einzelentscheidungen getroffen?

Nein

3. Art der gespeicherten Daten

Handelt es sich um besondere sensitive Daten gem. § 4 Abs. 3 DSG NRW?

Namensangaben:	Nein
Kommunikationsdaten:	Nein
Berufsdaten:	Nein
Meinungen zur Arzneimitteltherapie:	Nein

4. Schutzbedarf und Grundwerte

4.1 Risikoabschätzung

Qualitative Bewertung der Gefährdung der Grundwerte mit einer 3-stufigen Skala (normal, hoch, sehr hoch).

Namensangaben:	Normal
Kommunikationsdaten:	Normal
Berufsdaten:	Normal
Meinungen zur Arzneimitteltherapie:	Normal

Allgemeine Begründungen:

Man kann von einer sehr geringen bis normales Schutzbedarfkategorie ausgehen, weil:

> Das Verstößen gegen der Sicherheit der personenbezogene gespeicherten Daten kaum gesetzliche oder moralische Konsequenzen für die betroffenen haben würden.
>
> Eine Beeinträchtigung des Informationellen Selbstbestimmungsrecht durch den einzelnen als

tolerable bezeichnet werden kann.

Eine Beeinträchtigung der persönlichen Unversehrtheit nicht möglich scheint.

Die Vertraulichkeit, Verfügbarkeit und Integrität werden durch organisatorische und technische Maβnahmen gewährleistet.

5. Kreis der Betroffenen

Ärzte, Pharmakologen und weitere Experten mit fundierte Sachkenntnisse im verschiedenen Aspekten der Arzneimitteltherapie der pädiatrischen Herzinsuffizienz, die in Europa berufstätig sind.

6. Art regelmäßig zu übermittelnder Daten sowie deren Empfänger und Art und Herkunft regelmäßig empfangener Daten

6.1 Art regelmäßig zu übermittelnder Daten sowie deren Empfänger

Keine.

6.2 Art regelmäßig empfangener Daten sowie deren Herkunft

Keine.

7. Zugriffsberechtigten Personen oder Personengruppen

Der Projektbeteiligte in dem Institut für Klinische Pharmazie und Pharmakotherapie.

8. Technische und organisatorische Maßnahmen

Die dazugehörige Maßnahmen werden beim Electric Paper Evaluationssysteme GmbH (EvaSys®)angewendet, wie in dem unterschriebenen Vertrag mit der Heinrich-Heine-Universität Düsseldorf vereinbart.

9. Technik des Verfahrens

9.4 Eingesetzte Software (einschl. Standardvefahren)

EvaSys® Version 6.1

Excel® (nur anonymisierte Daten werden in diesem Software eingetragen).

R-Studio® (nur anonymisierte Daten werden in diesem Software eingetragen).

10. Fristen für die Berichtigung, Sperrung und Löschung gem. (§ 19 Abs. 1, 2 und Abs. 3 DSG NRW)

Frist für die Berichtigung (§ 19 Abs. 1 DSG NRW)

4 Monate (Umfrage Dauer, danach werden personenbezogenen Daten gelöscht).

Frist für die Sperrung (§ 19 Abs. 2 DSG NRW)

4 Monate (Umfrage Dauer, danach werden personenbezogenen Daten gelöscht).

Frist für die Löschung (§ 19 Abs. 3 DSG NRW)

Die Löschung der Daten, wird nach direktem Wunsch eines Teilnehmers geschehen. Die Löschung der Daten, die die Zuordnung von einen Teilnehmer zu den einzelnen Antworten erlauben könnten, wird spätestens nach Beendigung der Umfrage gemacht (4 Monate nach Anfang der Umfrage). Nach der Empfehlungen der Deutschen Forschungsgemeinschaft, werden die Originaldaten in der Institution für einen Zeitraum von 10 Jahren gespeichert, aber nur in anonymisierter Form.

11. Beabsichtigte Datenübermittlung an Drittstaaten (§ 17 DSG NRW)

Es wird keine Datenübermittlung an Drittstaaten stattfinden.

12. Organisation und Infrastruktur § 10 Abs. 3 DSG NRW

Siehe Anlage I.

13. Abschließende Bewertung des Fachbereichs

(Separates Dokument: *Abschließende datenschutzrechtliche Stellungnahme*)

14. Ergänzungen (Gewährleistet das Verfahren die Rechte der Betroffenen auf Auskunft, Widerspruch, Unterrichtung, Berichtigung, Sperrung und Löschung nach § 5 DSG NRW?)

Siehe Punkt 10. Jeder Teilnehmer wird zu Beginn der Teilnahme an der Umfrage die erforderliche Information durch die Einwilligungserklärung (Anlage II) erhalten.

15. Ergebnis[1]

Ergebnis der Vorabkontrolle durch den behördlichen/betrieblichen DSB

Das Verfahren wird der Schutzstufe NORMAL zugeordnet.

(X) Die technischen und organisatorischen Maβnahmen des Verfahrens sichern die Vertraulichkeit, die Integrität und die Verfügbarkeit der Daten des Betroffenen.

(X) Das Restrisiko ist tragbar.

( ) Die technischen und organisatorischen Maβnahmen des Verfahrens sichern die Vertraulichkeit, die Integrität und die Verfügbarkeit der Daten des Betroffenen nur unzureichend.

( ) Es sind folgende Maβnahmen zum Schutz der Grundwerte zu ergreifen:

29.5.15

[1] Ab diesem Punkt würde die Information vom Datenschutzbeauftragten ausgefüllt.

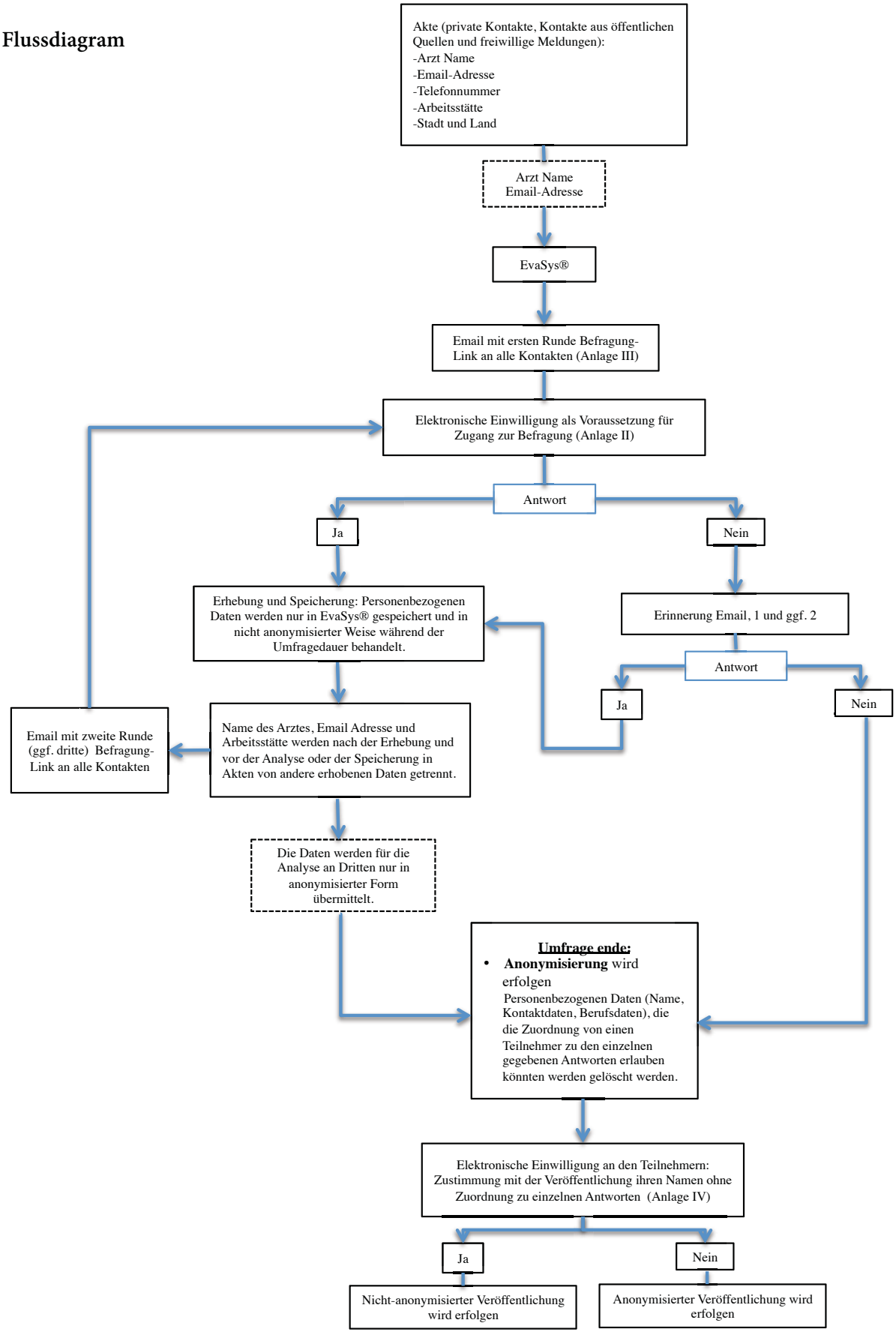
Das Verfahrensverzeichnis ist in Ordnung.

Es bestehen keine durchgreifenden datenschutzrechtlichen Bedenken gegen die Durchführung Ihres Projektes.

Das zur Erhebung der Umfragedaten verwendete System EvaSys® befindet sich derzeit noch in der datenschutzrechtlichen Vorabkontrolle, die im Rahmen eines anderen Projektes durchgeführt wird. Auf Grund der Schutzbedürftigkeit der Daten im Projekt LENA ist es aber vertretbar, dass Projekt LENA bereits vor der absehbaren datenschutzrechtlichen Abnahme des Systems EVAsys durchzuführen. Für das FP LENA ergeben sich hieraus zunächst keine weiteren datenschutzrechtlichen Auflagen.

Anlage I: Organisation und Infrastruktur § 10 DSG NRW

1. Flussdiagram



2. Durchführung

Die Ausführung der Vorschriften des Datenschutzgesetzes Nordrhein-Westfalen wird durch folgende technische und organisatorische Maßnahmen sichergestellt:

EvaSys® technische und organisatorische Maßnahmen (die dazugehörige Maßnahmen werden beim Electric Paper Evaluationssysteme GmbH EvaSys® angewendet, wie in dem unterschriebenen Vertrag mit der Heinrich-Heine-Universität Düsseldorf vereinbart).

Alle Betroffenen werden mit einer Einwilligungserklärung informiert und diese als Voraussetzung für die Teilnahme an der Umfrage zustimmen müssen.

Nur die genannten Zugriffsberechtigten Personen werden in der verantwortlichen Stelle das Passwort um Zugang zu den im EvaSys® erhobenen Daten haben.

Die erhobenen Daten werden nach dem Empfang und vor der Analyse oder Speicherung in Akten aufgenommen. Dabei werden der Name des Arztes, die zugehörige Email-Adresse und der Name des Krankenhauses von anderen Daten getrennt. Nach der Beendigung der Umfrage werden die Daten anonymisiert, das heißt, die EvaSys® Datei die eine Zuordnung der Antworten zu einer Person ermöglichen würde, wird gelöscht.

Appendix R: Delphi study - Data Protection Officer approval

Der Datenschutzbeauftragte

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

03. Juni 2015

Abschließende datenschutzrechtliche Stellungnahme

Elektronische Umfrage „Analysing the standard of care of paediatric heart failure across Europe through a Delphi process" – Studie im Rahmen des europäischen Forschungsprojektes LENA

Der Datenschutzbeauftragte der Heinrich-Heine-Universität Düsseldorf ist gebeten worden eine datenschutzrechtliche Stellungnahme zum oben genannten Forschungsvorhaben abzugeben.

Zu diesem Zweck war die Bereitstellung entsprechender Dokumente über den Inhalt sowie die Art und Weise der Durchführung der Studie sowie die Darstellung der Notwendigkeit zur Erhebung und Verarbeitung personenbezogener Daten der teilnehmenden Personen notwendig.

Frau Cristina Castro Diez wurden allgemein über die datenschutzrechtlichen Grundlagen wissenschaftlicher Forschung und speziell über die aus Sicht des Datenschutzrechtes NRW notwendigen Änderungen im Aufbau und Ablauf der Studie beraten.

Als verantwortliche Stelle der Umfrage wurde das Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf unter Leitung von Frau Prof. Dr. med. Läer festgelegt.

Nach Abschluss der datenschutzrechtlichen Prüfung wird folgendes festgestellt:

1. Die Notwendigkeit der Datenerhebung und der anschließenden Verarbeitung entspricht den Bestimmungen zur Datenverarbeitung für wissenschaftliche Zwecke gemäß § 28 DSG NRW.
2. Die Teilnehmer an der Umfrage werden umfassend über Inhalt, Zweck und Ablauf der Studie informiert. Sie werden über die jederzeit bestehende Möglichkeit

der Beendigung der Teilnahme ohne Angaben von Gründen informiert. Die Teilnehmer willigen der Speicherung, Verarbeitung und Veröffentlichung ihrer Daten elektronisch ein, wobei Namen und Arbeitsstätten nur von solchen Teilnehmern mit der Publikation der Ergebnisse veröffentlicht werden, die dieser Veröffentlichung freiwillig elektronisch zusätzlich zugestimmt haben. Die elektronische Einwilligung wird durch ein opt-in (die Interessenten müssen die Teilnahme an der Studie explizit bestätigen) realisiert. Hier wird zwar empfohlen, die elektronische Einwilligung durch ein double-opt-in oder zumindest durch ein confirmed opt-in zu ermöglichen, es bestehen aber keine durchgreifenden datenschutzrechtlichen Bedenken zu der hier gewählten Einwilligungslösung.

3. Die Datensparsamkeit ist insofern gegeben, als nur die notwendigen und geeigneten personenbezogenen Daten erhoben und verarbeitet werden und die Anonymisierung gemäß § 28 Abs. 3 DSG NRW so früh wie möglich erfolgt.

4. Der nach § 8 DSG NRW erforderliche Eintrag in das Verfahrensverzeichnis der Heinrich-Heine-Universität Düsseldorf wurde abschließend erstellt.
   Die Durchführung der Umfrage erfolgt mit Hilfe des an der Heinrich-Heine-Universität Düsseldorf bereits eingesetzten Befragungssystems EVAsys, welches sich derzeit allerdings noch in der datenschutzrechtlichen Vorabkontrolle gemäß § 10 DSG NRW befindet, die im Rahmen eines anderen Projektes durchgeführt wird. Auf Grund der Schutzbedürftigkeit der hier erhobenen Daten ist es aber vertretbar, das Projekt bereits vor der absehbaren datenschutzrechtlichen Abnahme des Systems EVAsys durchzuführen. Für die hier vorgesehene Umfrage ergeben sich hieraus zunächst keine weiteren datenschutzrechtlichen Auflagen.
   Das wissenschaftliche Team der Studie übernimmt aus dem System Evasys nur die für die Analyse notwendigen Umfrageantworten auf die eigenen Notebooks. Alle personenbezogene Daten wie Kontaktdaten, Name verbleiben auf dem Befragungssystem EVAsys. Die Auswertung der Umfrageantworten erfolgt auf den Notebooks mit Hilfe von MS Excel und R-Studio. Ohne Kenntnis der auf dem Befragungssystem EVAsys verbliebenen personenbezogenen Daten kann den auf die Notebooks übernommen Daten keine konkrete Person zugeordnet werden. Insofern wurde für die Verarbeitung der (Analyse-)Daten auf besondere Sicherheitsmaßnahmen, wie z.B. Verschlüsselung der Daten auf den Notebooks verzichtet.

5. Eine Trennung der personenbezogenen Daten von den Umfrageantworten findet gemäß des Ablaufplans der Untersuchung nur insofern statt, als dass die Umfrageantworten zum Zwecke der Auswertung von EvaSys auf die von den Wissenschaftlern benutzten Notebooks übertragen werden

   Eine Anonymisierung findet erst nach Auswertung der Umfrage statt, d.h. die nur noch auf dem Befragungssystem EVAsys vorhandenen personenbezogene Daten wie Kontaktdaten, Name werden unwiderruflich gelöscht.

   Diese Vorgehensweise ist durch § 28 Abs. 1 Satz 3 DSG NRW (Datenverarbeitung für wissenschaftliche Zwecke) gedeckt, da der Personenbezug auf dem System EVAsys gelöscht wird, sobald der Forschungszweck dies gestattet.

Es bestehen keine durchgreifenden datenschutzrechtlichen Bedenken gegen die Durchführung des Projektes.

gez. Kurt Finkbeiner

Appendix S: Delphi study - Ethics Committee approval

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF
ETHIKKOMMISSION der Medizinischen Fakultät

ETHIKKOMMISSION der Medizinischen Fakultät der Heinrich-Heine-Universität, Moorenstr. 5, 40225 Düsseldorf

Frau
Prof. Dr. med. Läer
Institut für Klinische Pharmazie und Pharmakotherapie

HIER

Prof. Dr. T. Hohlfeld

Telefon: (0211)81-19590
Sekretariat: (0211)81-19591
FAX: (0211)81-19592
Ethikkommission@med.uni-duesseldorf.de

26. Jun. 2015

FAX: 10741

Stets angeben:
Studiennummer: 5131

Sehr geehrte Frau Kollegin Läer,

die Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf hat Ihren Antrag mit dem Titel:

Analysing the standard or care of paediatric heart failure across Europe through a Delphi process

geprüft und beurteilt.

Nachdem Sie die Auflagen der Ethikkommission erfüllt haben, bestehen keine ethischen oder rechtlichen Bedenken gegen die Durchführung Ihrer Studie.

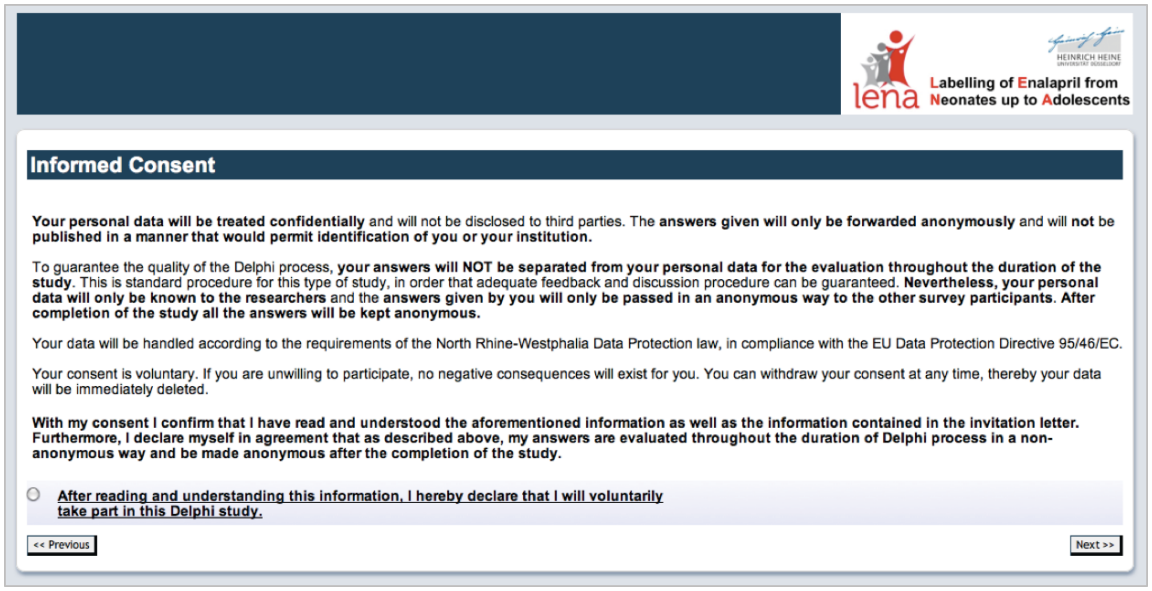
Nach Abschluss des Projektes bitte ich um Übersendung eines knappen Schlussberichtes oder einer abschließenden Publikation.

Für die Durchführung der Studie wünschen wir viel Erfolg!

Mit freundlichen Grüßen

Prof. Dr. Klaus-Dietrich Kröncke
i. A. der Kommission

Appendix T: Delphi study – Informed consent



lena
Labelling of Enalapril from Neonates up to Adolescents

Informed Consent

Your personal data will be treated confidentially and will not be disclosed to third parties. The **answers given will only be forwarded anonymously** and will **not** be **published in a manner that would permit identification of you or your institution.**

To guarantee the quality of the Delphi process, **your answers will NOT be separated from your personal data for the evaluation throughout the duration of the study**. This is standard procedure for this type of study, in order that adequate feedback and discussion procedure can be guaranteed. **Nevertheless, your personal data will only be known to the researchers** and the **answers given by you will only be passed in an anonymous way to the other survey participants**. **After completion of the study all the answers will be kept anonymous.**

Your data will be handled according to the requirements of the North Rhine-Westphalia Data Protection law, in compliance with the EU Data Protection Directive 95/46/EC.

Your consent is voluntary. If you are unwilling to participate, no negative consequences will exist for you. You can withdraw your consent at any time, thereby your data will be immediately deleted.

With my consent I confirm that I have read and understood the aforementioned information as well as the information contained in the invitation letter. Furthermore, I declare myself in agreement that as described above, my answers are evaluated throughout the duration of Delphi process in a non-anonymous way and be made anonymous after the completion of the study.

○ **After reading and understanding this information, I hereby declare that I will voluntarily take part in this Delphi study.**

<< Previous Next >>

Appendix U: Delphi study- Questionnaire round 2[1]

Delphi study on the pharmacotherapeutic management of paediatric heart failure: round 2

Welcome to the second round of the Delphi study on the pharmacological management of paediatric heart failure

Thank you for agreeing to participate in the second round of this Delphi process. Your responses will provide very valuable information.

As previously explained, **you will find feedback of the first round is presented for each statement** with the following structure:

- Frequencies of the answers given by the panel (percentage of experts that selected each answer option).
- Mean score and the 95% confidence interval around it for each of the statements.
- Summary of rationale/comments that were given to the statement.
- Further explanations by research team.

We would like to re-evaluate your level of agreement once again with these 7 statements in light of the provided feedback. Of course, you can select the same answer as before or change your position, if you consider it now to be more appropriate.

Please **try to answer the questionnaire in one session, otherwise your answers will not be sent correctly**. If you left the questionnaire open for more than 10 minutes without working on it, you will need to close it and re-start it by using your link again.

If you have any difficulty or questions do not hesitate to contact us at cristina.castro.diez@uni-duesseldorf.de

[1] Please note that the questionnaire was not distributed to participants in the present format but using web-survey platform EvaSys®

Angiotensin-converting enzyme inhibitors (ACE-I): Considerations for optimal dosage

3a. In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.

Feedback round 1

Answers frequency

Strongly disagree 7,7%
Disagree 30,8%
Neither agree/disagree 0%
Agree 46,2%
Strongly agree 15,4%

Consensus evaluation: Mean and 95% confidence interval

3,31 (2,59 - 4,03)

Comments given by experts disagreeing

Experts disagreeing with this statement gave comments with regard to individual patient aspects: patient age, specific diagnosis, severity of heart failure and the situation of having an out- or inpatient can fasten or slow the up-titration procedure.

Further explanations to the statement by the research team

This statement is based on a recommendation published in the supplement table of the paediatric guideline elaborated by the Canadian Cardiovascular Society (Kantor et al. Can J Cardiol. 2013.29:1535–52). The recommendation to increase the dose every 48h/ at 48h intervals was identified as the shortest guideline based recommended interval for up-titration in paediatric patients with heart failure.
Guidelines for adults (McMurray et al. *Eur Heart J.* 2012;33: 1787–1847) recommend: "double the dose at not less than 2-week intervals in the community. More rapid dose up-titration may be carried out in patients in hospital or who are otherwise closely monitored, tolerability permitting"
The statement presented here, similarly as recommendations given by guidelines, intends to suit the average patient/situation, thus assuming that physicians might act differently to meet individual patients needs.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

3b. In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.

Feedback round 1

Answers frequency

Strongly disagree 0%
Disagree 38,5%
Neither agree/disagree 23,1%
Agree 30,8%
Strongly agree 7,7%

Consensus evaluation: Mean and 95% confidence interval

3,08 (2,52 - 3,64)

Comments given by experts disagreeing

Experts disagreeing with this statement reported up-titrating dose in 25% steps, in fixed intervals of 0,1 mg/kg or not performing up-titration at all.

Comments given by experts agreeing

Experts agreeing reported doubling the dose at each up-titration step, unless patient clinical response requires another procedure.

Further explanations to the statement by the research team

This statement is based on the recommendation published in the ESC guideline for the management of heart failure in adults (McMurray et al. Eur Heart J. 2012;33: 1787–1847) and on the summary of product characteristics of ACE-I used for adult heart failure.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

4. If deterioration of the renal function occurred in a patient on ACE-I therapy, concomitant diuretic medication should be readjusted before deciding to down titrate/stop up-titrating the ACE-I.

Feedback round 1

Answers frequency

Strongly disagree 7,7%
Disagree 23,1%
Neither agree/disagree 0%
Agree 61,5%
Strongly agree 7,7%

Consensus evaluation: Mean and 95% confidence interval

3,38 (2,73 - 4,03)

Comments given by experts disagreeing

Experts disagreeing with this statement explained proceeding either first lowering the dose of ACE-I or stopping the therapy with it.

Comments given by experts agreeing

Experts agreeing confirmed to lower the diuretic dose before lowering the ACE-I dose.

Further explanations to the statement by the research team

This statement is supported by the recommendation of considering first reducing the dose of diuretics, if no signs of congestion exist, when deterioration of renal function is detected in patients on ACE-I published in the ESC guideline for the management of heart failure in adults (McMurray et al. Eur Heart J. 2012;33: 1787–1847).

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

5. If no adverse events occur, ACE-I dose should be increased to the target dose, even if the patient has already experienced improvement with a lower dose.

Feedback round 1

Answers frequency

Strongly disagree 7,7%
Disagree 46,2%
Neither agree/disagree 15,4%
Agree 15,4%
Strongly agree 15,4%

Consensus evaluation: Mean and 95% confidence interval

2,85 (2,15 - 3,55)

Comments given by experts disagreeing

Experts disagreeing reported remaining at a low dose if an improvement has been achieved.

Comments given by experts neither agreeing nor disagreeing

Experts selecting this answer option reported however generally trying to achieve the target dose.

Further explanations to the statement by the research team

This statement is supported by current recommendations for the use of ACE-I in adult patients with heart failure. ESC guideline (McMurray et al. Eur Heart J. 2012;33: 1787–1847) recommends aiming "for target dose or, failing that, the highest tolerated dose". These target doses are those that were used and showed an improvement in survival in key randomized trials. Controversy regarding the most appropriate dosing strategy for ACE-I in adults exists. Nevertheless, evidence suggests that titration according to clinical response is not an appropriate approach.

The use of ACE-I for the paediatric heart failure population is largely supported on this adults' evidence. There are no systematic data addressing this topic in the paediatric population.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

6. In order to maximise the accuracy of the ACE-I dose given, the use of different types of formulations for a patient throughout the duration of the treatment should be avoided.

Feedback round 1

Answers frequency

Strongly disagree 7,7%
Disagree 15,4%
Neither agree/disagree 15,4%
Agree 38,5%
Strongly agree 23,1%

Consensus evaluation: Mean and 95% confidence interval

3,54 (2,85 - 4,23)

Comments given by experts neither agreeing nor disagreeing

Experts selecting this answer option expressed not identifying this topic as a relevant treatment issue.

Comments given by experts agreeing

Comments were given as a saying: "Never change a winning team".

Further explanations to the statement by the research team

As in European countries ACE-I are often prescribed off-label and no commercialized paediatric appropriate formulations exist, pharmacies provide formulations individually prepared for the patients. These formulations are less standardized than licensed products. Sometimes parents have to crush tablets and dissolute them for administration to their child. All these procedures are potential causes of variability in the administered dose.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

ACE-I for the management of congenital heart diseases

7. Paediatric patients with asymptomatic mitral or aortic regurgitation benefit from ACE-I therapy.

Feedback round 1

Answers frequency

Strongly disagree 7,7%
Disagree 7,7%
Neither agree/disagree 23,1%
Agree 61,5%
Strongly agree 0%

Consensus evaluation: Mean and 95% confidence interval

3,38 (2,86 - 3,9)

Comments given by experts disagreeing

Experts disagreeing with this statement reported considering evidence supporting this practice is lacking. Furthermore, in their opinion, decision should be based in additional aspects such as degree of regurgitation, patient age or surgery timing.

Comments given by experts neither agreeing nor disagreeing

Similarly to experts disagreeing, physicians selecting this answer option expressed not being sure of evidence supporting this practice. Furthermore, they considered that also additional disease parameters have to be taken in consideration when deciding if a patient with asymptomatic valve regurgitation should or should not receive ACE-I therapy.

Comments given by experts agreeing

Experts agreeing with this statement consider that the pathophysiology of valve regurgitation supports this practice.

Further explanations to the statement by the research team

The weight of evidence supporting this statement is low. Nevertheless, a randomly controlled study (Mori Y et al. J Am Coll Card. 2000;36:270–275) showed improvement of ventricular echocardiographic indexes in asymptomatic children with mitral and aortic regurgitation under ACE-I treatment.

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy

12. Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).

Feedback round 1

Answers frequency

Strongly disagree 0%
Disagree 38,5%
Neither agree/disagree 15,4%
Agree 30,8%
Strongly agree 15,4%

Consensus evaluation: Mean and 95% confidence interval

3,23 (2,6 - 3,86)

Comments given by experts disagreeing

Experts disagreeing reported introducing the therapy with aldosterone antagonists early on.

The routinely use of spironolactone as a diuretic in combination with the loop diuretic furosemide in all symptomatic heart failure patients with dilated cardiomyopathy was also reported.

Comments given by experts neither agreeing nor disagreeing

Experts selecting this answer option explained that the decision depends for them on the severity of the disease.

Further explanations to the statement by the research team

This statement is based on the evidence supporting the use of aldosterone antagonists for adult patients with heart failure. No evidence exists at the moment to encourage or discourage this practice in the paediatric population. Guidelines for the management of heart failure in adult patients (McMurray et al. Eur Heart J. 2012;33: 1787–1847) recommend the use of aldosterone antagonists "for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker". The Canadian Cardiovascular Society has integrated this recommendation into their paediatric guideline (Kantor et al. Can J Cardiol. 2013;29:1535–52).

Please select one item.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Rationale/Comment:

XIII. Publications used in the present thesis and own contribution

Publications

1. Castro Díez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I, Makowski N, Male C, Bajcetic M, van der Meulen M, de Wildt SN, Ablonczy L, Szatmári A (†), Klingmann I, Walsh J, Läer S. **Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey.** Accepted 2nd December 2018 in BMJ Paediatrics Open. Status: Awaiting publication

   Own contribution:

   Literature review on survey research methodology and questionnaires design best practice. Design of survey research plan. Literature review on paediatric heart failure pharmacotherapy. Recruitment of an expert panel that was to support survey and questionnaire design. Initial selection of questionnaire contents; drafting of questionnaire (list of questions, instructions for participants, cover letters); elaboration of plan for and execution of questionnaire pre- and pilot-testing; elaboration of questionnaire final version. Design and conduction of reliability and validity testing; supervision of analysis of results; interpretation of findings. Elaboration of survey study Data Protection plan. Preparation of documents for Ethics Committee. Selection of target population, inclusion and exclusion criteria. Elaboration of contacts list: identification of paediatric cardiology centres and physicians across Europe, and their contact data. Web-survey platform test and selection. Integration of survey and contacts into web-survey platform. Elaboration of statistical analysis manual. Distribution of questionnaire. Data processing: data extraction from web-survey platform, data encoding and preparation of ready-to-analyse data. Interpretation of findings. Elaboration of survey study report FP7 LENA WP12 for the European Commission. Drafting of the paper and elaboration of final version.

2. Castro Díez C, Khalil F, Makowski N, Schwender H, Jovanovic I, Dalinghaus M, Walsh J, van der Meulen M, Bajcetic M, de Wildt SN, Läer S. **Pharmacotherapy in paediatric heart failure: a Delphi process**. Submitted 31st October 2018 to Cardiology in the Young. Status: under review.

   Own contribution:

   Literature review on Delphi process methodology best practice. Design of Delphi process research plan. Selection of questionnaire contents. Design of questionnaire structure, drafting of questionnaire (list of questions, instructions for participants, cover letters). Elaboration of questionnaire final version. Preparation of questionnaire for the second round of the Delphi study. Elaboration of Delphi study Data Protecion plan. Preparation of documents for Ethics Committee. Selection of study population: criteria, sample size and sampling method. Elaboration of contacts list. Web-survey platform test and selection. Supervision of the integration of Delphi questionnaire and contacts into web-survey platform. Elaboration of statistical analysis manual. Distribution of questionnaire in first and second study round. Data processing: data extraction from web-survey platform, data encoding and preparation of ready-to-analyse data. Interpretation of findings. Elaboration of Delphi study report FP7 LENA WP 12 for the European Commission. Drafting of the paper and elaboration of final version.

XIV. Trainings and other scientific works during the PhD

iGRAD seminars at the Heinrich-Heine-University Düsseldorf

11/2017	Work in Heterogeneous Teams
04/2015	Get into Teaching
02/2015	Scientific Writing
03/2014	Gute Wissenschaftliche Praxis

Publications

van der Meulen M, Dalinghaus M, Burch M, Szatmari A, Castro Diez C, Khalil F, Swoboda V, Breur J, Bajcetic M, Jovanovic I, Lagler FB, Klingmann I, Laeer S, de Wildt SN. How safe are ACE-I in children? Arch Dis Child. 2018 Jan;103(1):106-109.

Posters with oral presentation

Castro Díez C, Khalil F, Dalinghaus M, van der Meulen M, de Wildt SN, Jovanovic I, Bajcetic M, Burch M, Male C, Klingmann I, Szatmári A, Ablonczy L, Schwender H, Läer S. Pharmacological management of paediatric heart failure: results of a European survey. Annual Meeting of the Association for European Paediatric and Congenital Cardiology (Rome, 1-4 June 2016)

Posters

Castro Díez C, Khalil F, Dalinghaus M, van der Meulen M, de Wildt SN, Jovanovic I, Bajcetic M, Burch M, Male C, Klingmann I, Szatmári A, Ablonczy L, Schwender H, Läer S. Design of a European survey on the pharmacological management of paediatric heart failure. European Society For Developmental Perinatal And Pediatric Pharmacology Congress (Belgrade, 23-26 June 2015)

Castro Díez C, Makowski N, Khalil F, Dalinghaus M, van der Meulen M, de Wildt SN, Jovanovic I, Bajcetic M, Burch M, Male C, Klingmann I, Szatmári A, Ablonczy L, Schwender H, Läer S. Standard of care for children with heart failure in Europe: results of a survey and a subsequent Delphi questionnaire. European Society For Developmental Perinatal And Pediatric Pharmacology Congress (Leuven, 20 -23 June 2017).