# The CERTAIN Registry

## Registry for Paediatric Kidney Transplantation

**Britta Höcker, Alexander Fichtner, Antonia H. Bouts, Kai Krupka, Lars Pape, Jan U. Becker and Burkhard Tönshoff**

on behalf of the CERTAIN Research Team,
the German Society of Paediatric Nephrology (GPN),
the European Society for Paediatric Nephrology (ESPN) ,
and Eurotransplant, Leiden, The Netherlands

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

gefördert durch DIETMAR HOPP STIFTUNG

**www.certain-registry.eu**

# Overview

1. **The CERTAIN Registry**
2. **Ongoing projects**
3. **Outlook: nephropathology module**

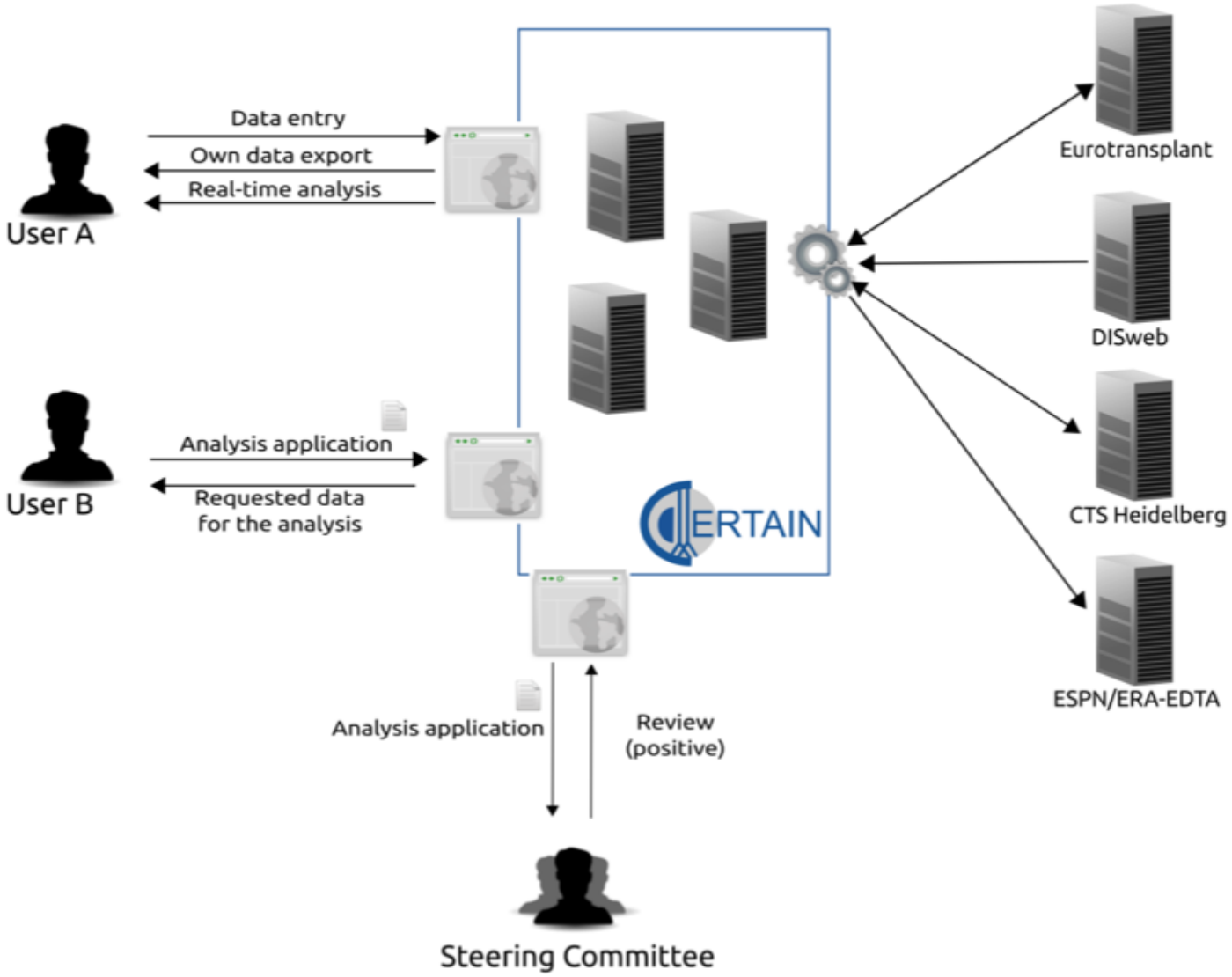
# Overview

1. **The CERTAIN Registry**
2. Ongoing projects
3. Outlook: nephropathology module

# Background

- The results of paediatric kidney transplantation have improved markedly in the last decade.
- However, a number of relevant clinical problems remain. These unmet clinical needs require intense collaborative and interdisciplinary clinical research.
- In 2010, we thus founded the **C**ooperative **E**uropean Paediatric **R**enal **T**ransplA**N**t **IN**itiative (CERTAIN; www.certain-registry.eu) as a European research network built on a novel, web-based registry.

# Data flow


Data entry
Own data export
Real-time analysis
User A
Analysis application
Requested data
for the analysis
User B
ERTAIN
Eurotransplant
DISweb
CTS Heidelberg
ESPN/ERA-EDTA
Analysis application
Review
(positive)
Steering Committee

# Activities linking with other registries

## ESPN/ERA-EDTA Registry

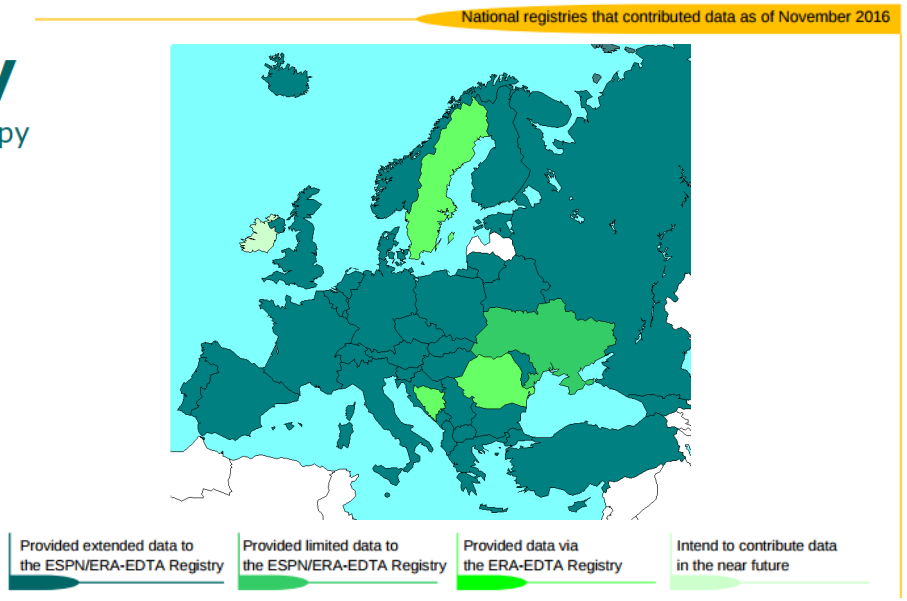
European Registry for Children on Renal Replacement Therapy

**Since 2012 IT interface between CERTAIN and ESPN/ERA-EDTA Registry:**

**Tool for ESPN Working Group "Renal Transplantation"**

www.espn.org

european society for paediatric nephrology




## ERKNet

The European Rare Kidney Disease Reference Network

European Reference Networks

**Link to CERTAIN Research Network envisaged**

www.erknet.org

# CERTAIN workshops and newsletter

european society for paediatric nephrology

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

European Reference Network for rare or low prevalence complex diseases

Network Kidney Diseases (ERKNet)

## Newsletter 2/2018

Dear colleagues,

this newsletter will update you on the recent publications from the CERTAIN Registry and on-going projects (see our website www.certain-registry.eu). Since many of the CERTAIN colleagues are also members of the ESPN working group "Transplantation" and/or of the ERKNet working group "Renal Transplantation", we decided to issue one newsletter for all three initiatives to bundle the forces. Many thanks to all of you for your contribution to previous and ongoing projects!

Yours, Burkhard Tönshoff and Lars Pape
Burkhard.Toenshoff@med.uni-heidelberg.de; Pape.Lars@mh-hannover.de

### Documentation and centres

More than 2150 patients from 60 centres in 17 countries are currently enrolled into the CERTAIN Registry. We are very grateful to all of you who contributed to this great success. Since the last newsletter one new centre joined the CERTAIN family: Lyon (France). For German centres in conjunction with the curatorship for home dialysis and transplantation (KfH), data entry will soon be facilitated by an interface between DISweb and CERTAIN.

### Save the date

The next meeting of our combined working groups will take place during the upcoming ***ESPN congress*** in ***Antalya, Turkey*** on Thursday, October 4, from 14:30 to 15:30 in Hall 2. The agenda:
14:30 - 14:45 Urinary proteomics to diagnose chronic antibody-mediated rejection in pediatric kidney transplantation – an analysis of the IM-MRES-CERTAIN trial *Lars Pape, Hannover*
14:45 - 15:00 Incidence, treatment and outcome of recurrent focal-segmental glomerulosclerosis after paediatric kidney transplantation in Europe *Antonia Bouts, Amsterdam*
15:00 - 15:15 Long-term outcome after pediatric combined liver and kidney transplantation: A CERTAIN Registry analysis *Florian Brinkert, Hamburg*
15:15 - 15:30 Antibody-mediated Rejection in European Paediatric Renal Trans-plant Recipients: Incidence, Risk Factors and Outcome *Alexander Fichtner and Burkhard Tönshoff, Heidelberg*

The ***40th Symposium*** of the ***CERTAIN Study Group*** will take place in ***Heidelberg, December 7 - 8, 2018.*** Online-registration will be available in September 2018.

### Manuscripts recently published or submitted

1. Höcker B, Schneble L, Murer L, Carraro A, Pape L, Kranz B, Oh J, Zirngibl M, Dello Strologo L, Büscher A, Weber LT, Awan A, Pohl M, Bald M, Printza N, Rusai K, Peruzzi L, Topaloglu R, Fichtner A, Krupka K, Köster L, Bruckner T, Schnitzler P, Hirsch H, Tönshoff B. ***Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study.*** Transplantation 2018, in press

2. Höcker B, Schneble L, Murer L, Carraro A, Pape L, Kranz B, Oh J, Zirngibl M, Dello Strologo L, Büscher A, Weber LT, Awan A, Pohl M, Bald M, Printza N, Rusai K, Peruzzi L, Topaloglu R, Fichtner A, Krupka K, Köster L, BrucknerT, Schnitzler P, Hirsch HH, Tönshoff B. ***JC polyomavirus replication and associated disease in pediatric renal transplantation: An international CERTAIN Registry study.*** Pediatr Nephrol 2018 https://doi.org/10.1007/s00467-018-4029-9.

3. Kreuzer M, Prüfe J, Tönshoff B, Pape L. ***Survey on Management of Transition and Transfer From***

## CERTAIN workshop

1. German Society of Paediatric Nephrology (GPN) congress
2. European Society for Paediatric Nephrology (ESPN) congress
3. Symposium of the "Interdisciplinary Study Group Renal Transplantation in Paediatrics"

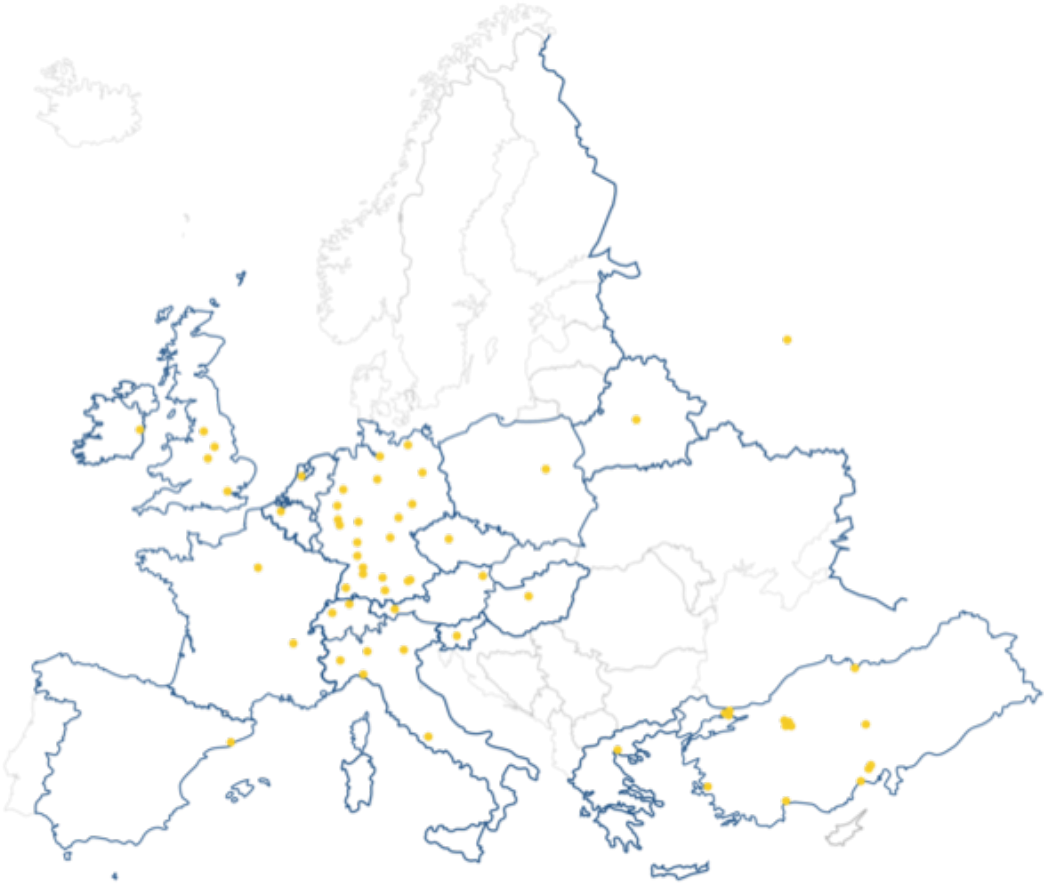
## CERTAIN newsletter

# Data set

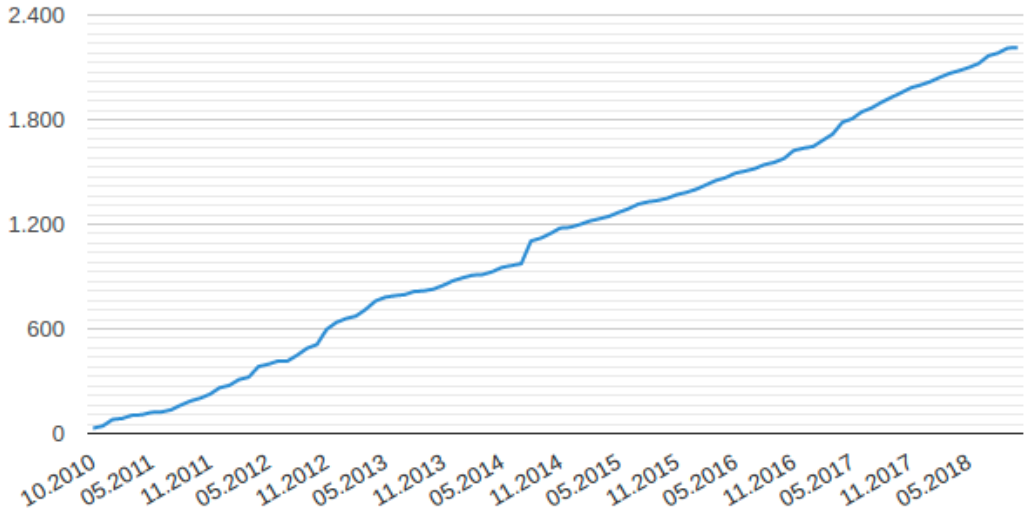
| **Minimal data set** | | **Extended data set** | |
|---|---|---|---|
| General data | Medication | Vaccination | Study |
| History | Drug monitoring | 24 hr blood pressure | |
| Donor | Laboratory | Psychosocial data | |
| Surgery | Immunology | | |
| Anthropometry | Infectiology | | |
| Graft function | Rejection | | |
| | Biopsy | | |
| | Complication | | |
| | Hospitalisation | | |

# Participating centres

- **62 participating centres in 18 countries**
  - Austria (2)
  - Belarus (1)
  - Belgium (1)
  - Czech Republic (1)
  - France (2)
  - Germany (22)
  - Greece (1)
  - Hungary (1)
  - Ireland (1)
  - Italy (5)
  - Poland (1)
  - Russia (1)
  - Slovenia (1)
  - Spain (1)
  - Switzerland (2)
  - The Netherlands (1)
  - Turkey (14)
  - United Kingdom (4)
- **194 registered users**

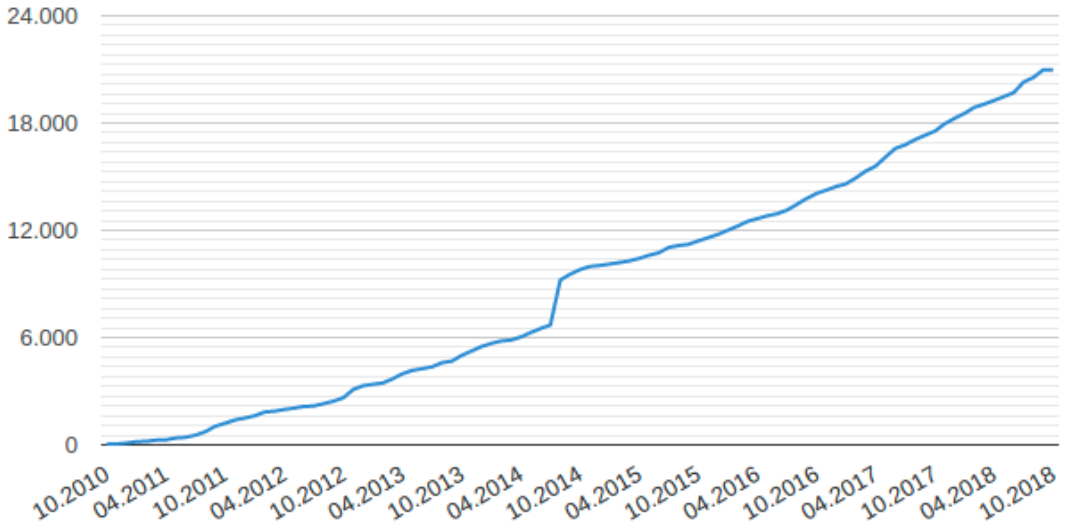


# Enrolled patients and documented visits




**Enrolled patients 2,212**

**Documented visits 20,987**



# Finalised scientific projects

| Title | Author | Journal |
|---|---|---|
| 1. Epidemiology of and risk factors for BK polyomavirus replication and nephropathy in pediatric renal transplant recipients: an international CERTAIN Registry study | Höcker B et al. | Transplantation 2018 |
| 2. JC polyomavirus replication and associated disease in pediatric renal transplantation: an international CERTAIN Registry study | Höcker B et al. | Pediatr Nephrol 2018 |
| 3. Survey on management of transition and transfer from pediatric- to adult-based care in pediatric kidney transplant recipients in Europe | Kreutzer M et al. | Transplant Direct 2018 |
| 4. Outcome of renal transplantation in small infants: a match-controlled analysis. | Weitz M et al. | Pediatr Nephrol 2018 |
| 5. Vaccination titres pre- and post-transplant in paediatric renal transplant recipients and the impact of immunosuppressive therapy | Höcker B et al. | Pediatr Nephrol 2018 |
| 6. Incomplete vaccination coverage in European children with end-stage kidney disease prior to renal transplantation | Höcker B et al. | Pediatr Nephrol 2018 |
| 7. Dyslipidemia after pediatric renal transplantation - the impact of immunosuppressive regimens | Habbig S et al. | Pediatr Transplant 2017 |
| 8. Cytomegalovirus infection in pediatric renal transplantation and the impact of chemoprophylaxis with (val-) ganciclovir | Höcker B et al. | Transplantation 2016 |
| 9. Impact of everolimus and low-dose cyclosporin on cytomegalovirus replication and disease in pediatric renal transplantation | Höcker B et al. | Am J Transplant 2016 |
| 10. Efficacy and safety of an everolimus- vs. a mycophenolate mofetil-based regimen in pediatric renal transplant recipients | Brunkhorst LC et al. | PLoS One 2015 |
| 11. Longitudinal growth on an everolimus- versus an MMF-based steroid-free immunosuppressive regimen in paediatric renal transplant recipients | Billing H et al. | Transpl Int 2013 |
| 12. Urinary proteomics to diagnose chronic antibody-mediated rejection in pediatric kidney transplantation | Kanzelmeyer NK et al. | *Submitted* |
| 13. Arterial hypertension and the use of antihypertensive medication in pediatric renal transplant patients: an analysis of the CERTAIN Registry | Melk A et al. | *In preparation* |

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| 2. JC polyomavirus replication and associate… …ediatric renal t… international CERTAIN Registry study | Höcker B et al. | Pediatr Nephrol 2018 |
| 3. Survey on management of t… …n … …l care in pediatric kidney transpl… | Kreutzer M et al. | Transplant Direct 2018 |
| 4. Outcome of re… …all … …ned …nalysis. | W… | …ediatr Nephrol 2018 |
| 5. Vaccina… …e-tra… …nal t… …cipients and th… im… …ssiv… | | Pediatr Nephrol 2018 |
| 6. Incor… …nation coverag… …n chi… …dne… to rena… …nsplantation | …ker B et al. | Pediatr Nephrol 2018 |
| 7. Dyslipidemia after pediatric renal t… …pact … regimens | Habbig S et al. | Pediatr Transplant 2017 |
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| 9. Impact of everolim… …dose … …galovirus replication and disea… in pediatric renal tr… …ntat… | Höcker B et al. | Am J Transplant 2016 |
| 10. Efficacy and safety of an everoli… …con… …fetil-based reg… pediatric renal transplant recipie… | …nkhorst LC et al. | PLoS One 2015 |
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Graft rejection

Immunosuppression

Transplant outcome

Cardiovascular complications

Vaccinations

Infections

# Ongoing prospective studies

| Title | PI |
| --- | --- |
| **IMMRES Study**<br>Immune response of paediatric renal transplant recipients challenged by sensitization, vaccination or non-adherence: cross-sectional and prospective analyses of the international CERTAIN Registry cohort | Pape L |
| **HPVaxResponse Study**<br>Prevention of human papillomavirus (HPV) infection in paediatric kidney and liver transplant recipients and in paediatric patients with advanced chronic kidney disease: a prospective, observational multi-centre vaccine surveillance study<br>**clinicaltrials.gov NCT03100682** | Höcker B |

# Ongoing registry analyses

| Title | PL |
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| 1. Antibody-mediated rejection in European Paediatric Renal Transplant Recipients: Incidence, Risk Factors and Outcome | Fichtner A<br>Heidelberg |
| 2. Proteinuria as a non-invasive marker for renal allograft histology and graft failure in paediatric renal transplant recipients | Büscher A<br>Essen |
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3. Outlook: nephropathology module

# Antibody-mediated Rejection in European Paediatric Renal Transplant Recipients: Prevalence, Risk factors and Outcome

## A CERTAIN interim analysis

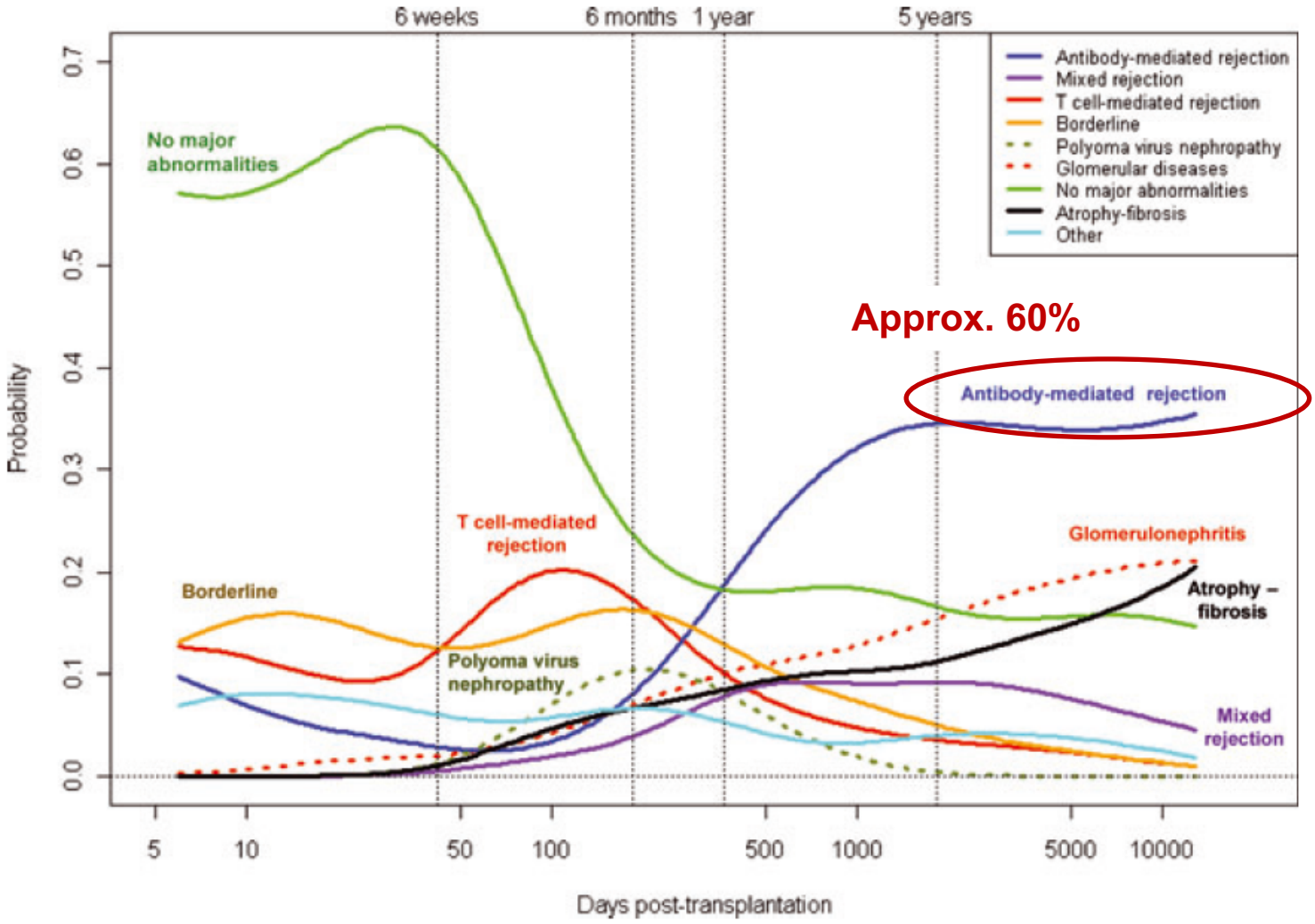
Alexander Fichtner, Caner Süsal, Britta Höcker, Jan Becker, Lars Pape, Stephen Marks, Luca dello Strologo, Kai Krupka, Lennart Köster, Members of the CERTAIN Research Network, Burkhard Tönshoff

For the CERTAIN Research Community and Interdisciplinary Study Group ”Renal Transplantation in Paediatrics“

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

gefördert durch DIETMAR HOPP STIFTUNG

# Biopsy-proven causes of graft loss in adults




Sellares *et al,* AJT 2012

# Rationale

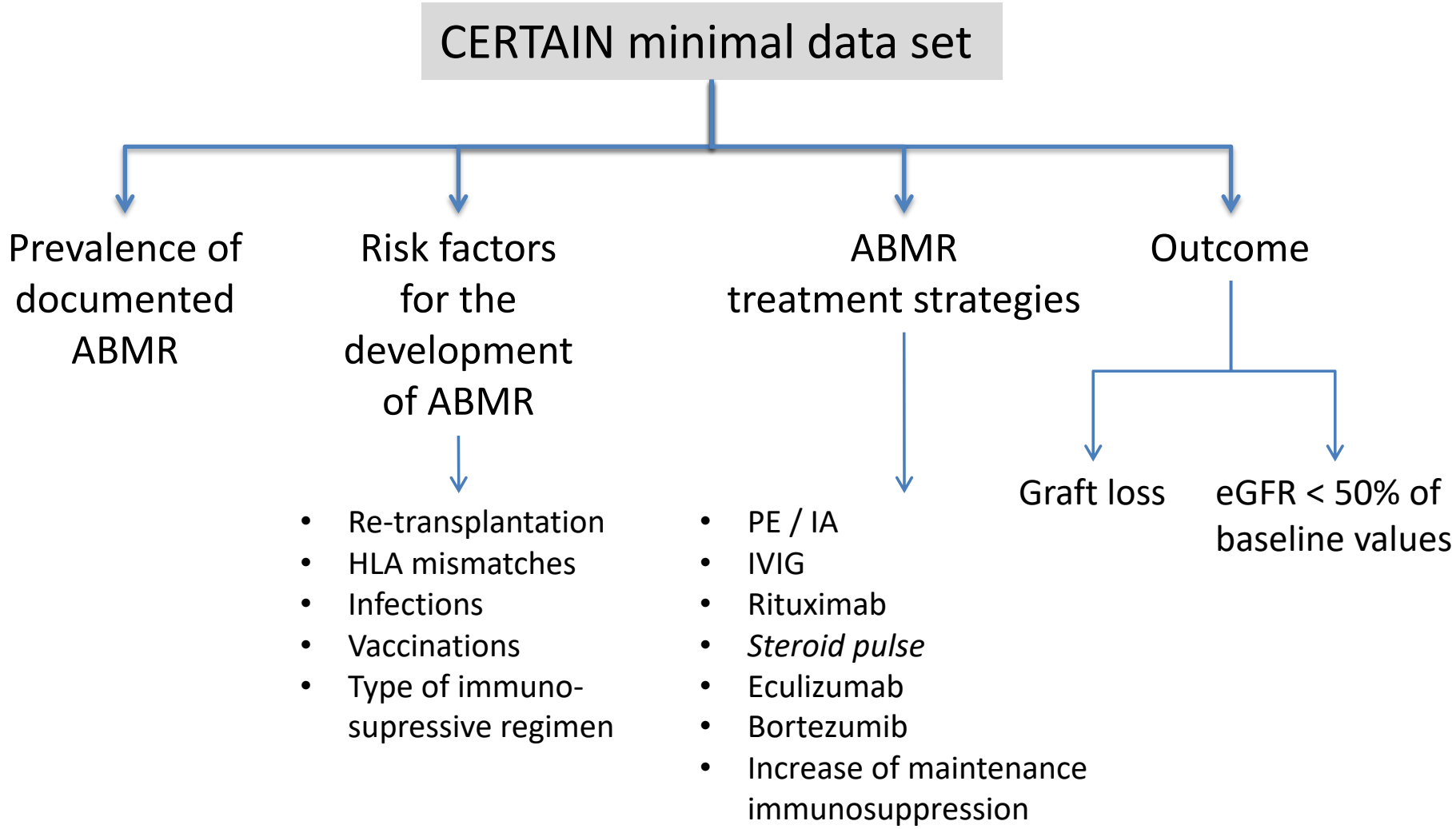
- Representative data on prevalence and outcome of ABMR in paediatric renal transplant recipients are limited

- Results from adult studies cannot necessarily be extrapolated to the paediatric population because of
  - Different immune biology
  - Different underlying diseases
  - Different risk profiles
    - Immunisation events: infections, vaccinations
    - Necessity of re-transplantation due to higher life expectancy
  - Efficacy and safety of treatment may not be directly translated from adults to children

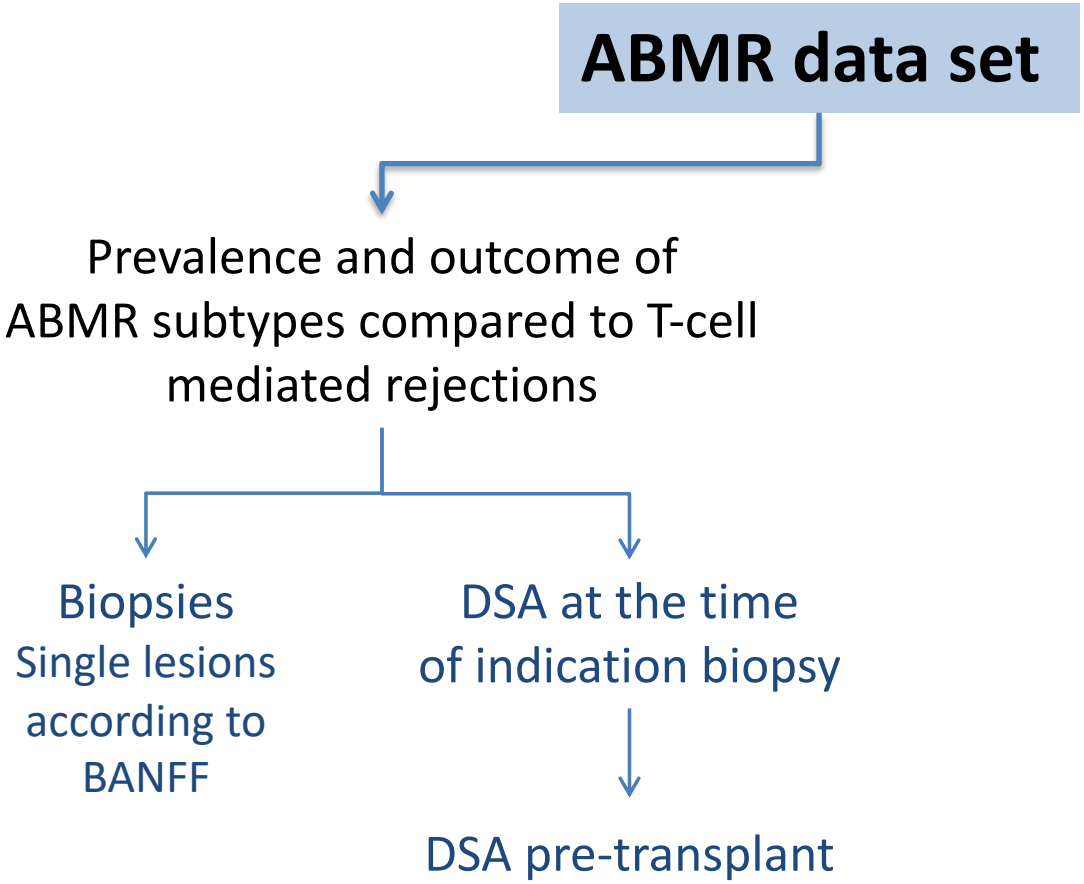
# Study Aims

- To describe the **prevalence** of different ABMR subtypes in European paediatric renal transplant recipients
- To analyze **risk factors** associated with the development of ABMR
- To describe different **treatment strategies** of ABMR
- To determine the **outcome** of ABMR

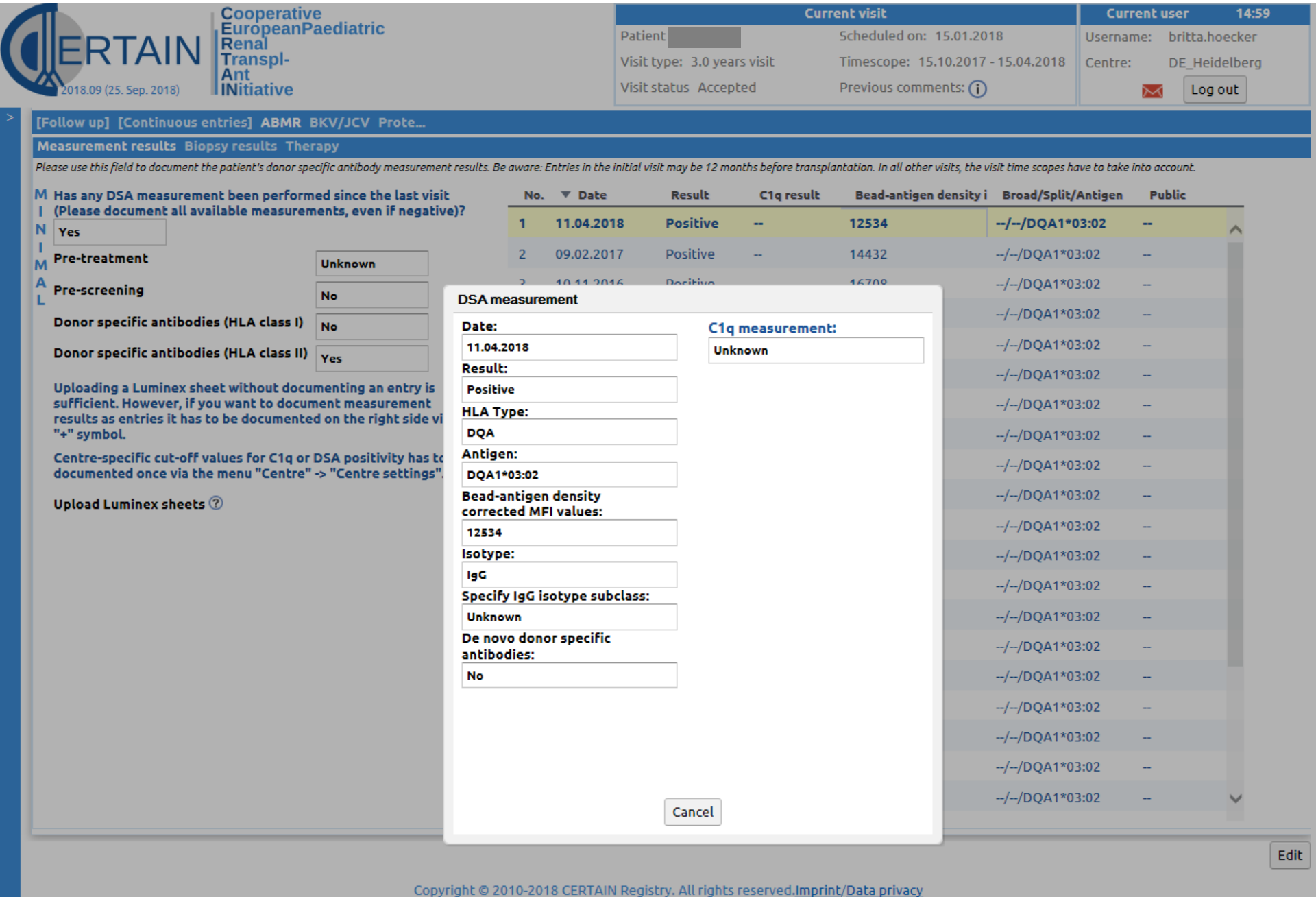
# Study design



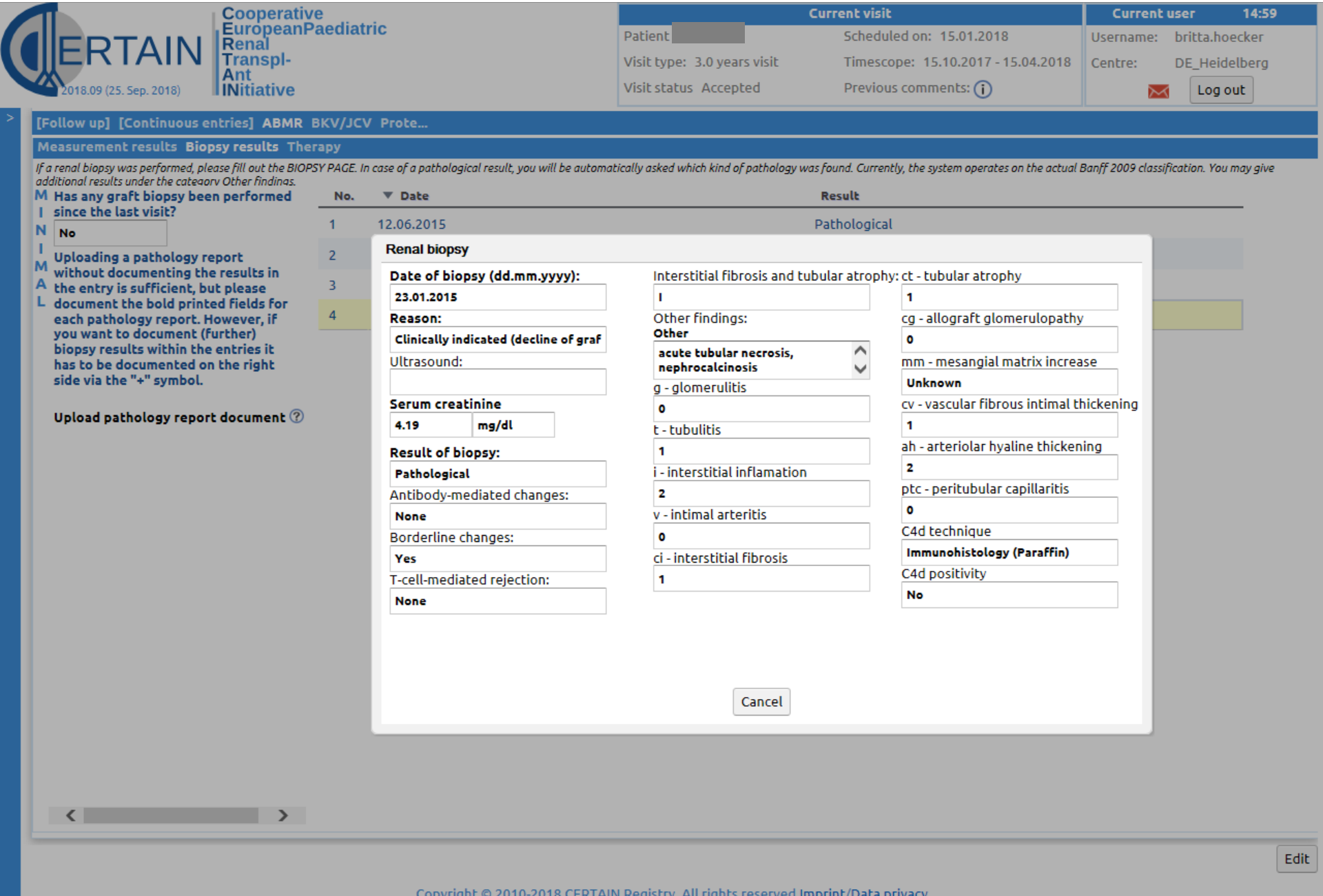
# Biopsy specificities



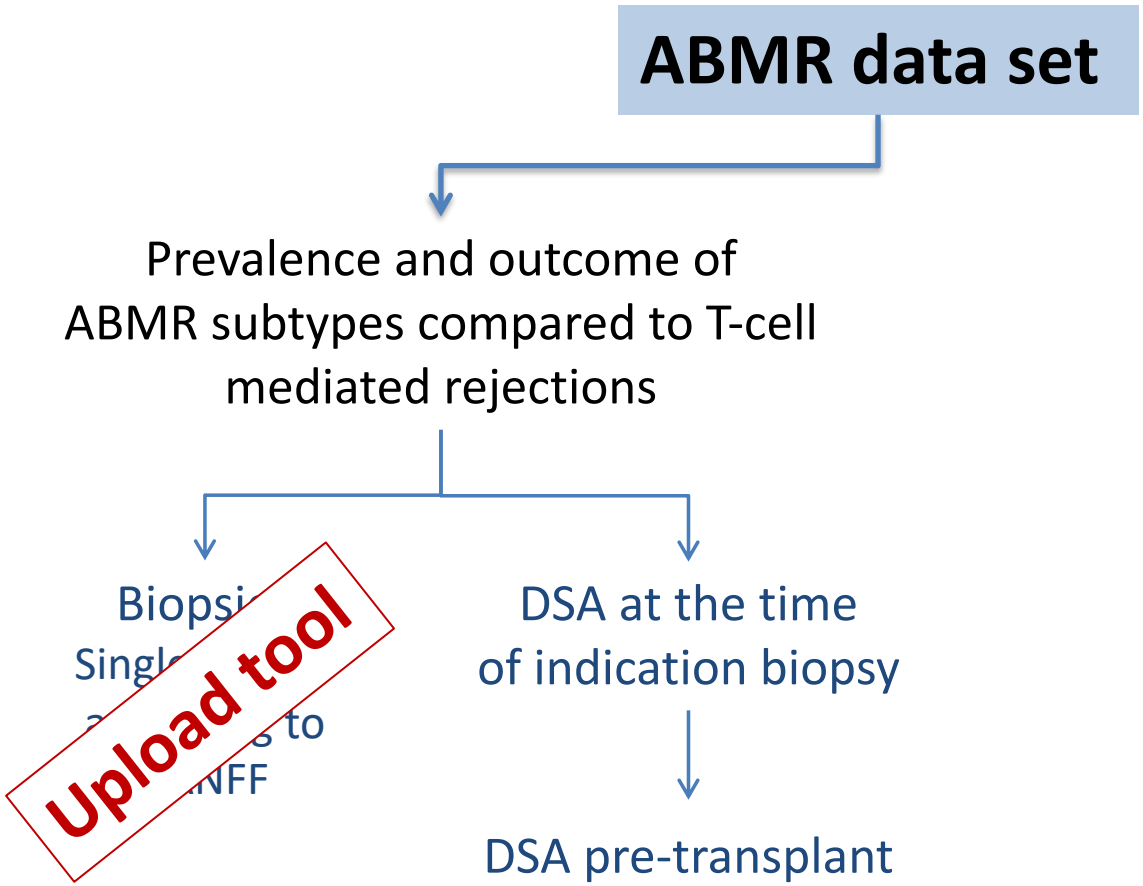
# Donor-specific HLA antibodies (DSA)



# Histopathological results



# Biopsy specificities



# Treatment

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative
2018.09 (25. Sep. 2018)

| Current visit | | Current user | 14:59 |
|---|---|---|---|
| Patient [redacted] | Scheduled on: 15.01.2018 | Username: | britta.hoecker |
| Visit type: 3.0 years visit | Timescope: 15.10.2017 - 15.04.2018 | Centre: | DE_Heidelberg |
| Visit status Accepted | Previous comments: | | Log out |

[Follow up] [Continuous entries] ABMR BKV/JCV Prote...

Measurement results Biopsy results **Therapy**

*Please use this field to document the patient's ABMR therapy. Be aware: Entries in the initial visit may be 12 months before transplantation. In all other visits, the visit time scopes have to take into account.*

**Has any treatment of DSA been performed since the last visit?**

MINIMAL

*Immunosuppressive medication*

| | |
|---|---|
| **Dose increase of maintenance immunosuppression** | **No** |
| **Change of maintenance immunosuppression** | **No** |
| **Steroid boli** | **No** |

*Specific therapy*

| | |
|---|---|
| **Plasmapheresis** | **No** |
| **Immunoadsorbtion** | **No** |
| **ATG** | **No** |
| **Rituximab** | **No** |
| **Bortezumib** | **No** |
| **Eculizumab** | **No** |
| **Intravenous immunoglobulin** | **No** |
| **Other therapy** | **No** |

**Any additional treatment has to be documented on the right side via the "+" symbol.**

| No. | Substance | Entry type | ▼ Date | Dose |
|---|---|---|---|---|
| 1 | Immunoadsorbtion | Stop | 23.09.2015 | -- |
| 2 | Bortezumib | Single dose | 20.08.2015 | 75[mg] |
| 3 | Bortezumib | Single dose | 17.08.2015 | 75[mg] |
| 4 | Bortezumib | Single dose | 13.08.2015 | 75[mg] |
| 5 | Bortezumib | Single dose | 10.08.2015 | 75[mg] |
| 6 | Bortezumib | Single dose | 02.05.2015 | 1.3[mg/m²/d] |
| 7 | Bortezumib | Single dose | 28.04.2015 | 1.3[mg/m²/d] |
| 8 | Immunoadsorbtion | New | 30.03.2015 | -- |
| 9 | Immunoadsorbtion | Single dose | 28.03.2015 | -- |
| 10 | Immunoadsorbtion | Single dose | 27.03.2015 | -- |
| 11 | Immunoadsorbtion | Single dose | 26.03.2015 | -- |
| 12 | Plasmapheresis | Single dose | 25.03.2015 | -- |
| 13 | Plasmapheresis | Single dose | 24.03.2015 | -- |
| 14 | Methylprednisolone | Stop | 28.02.2015 | 100[mg/m²/d] |
| 15 | Methylprednisolone | Change | 27.02.2015 | 100[mg/m²/d] |
| 16 | Methylprednisolone | Change | 25.02.2015 | 200[mg/m²/d] |
| 17 | Methylprednisolone | New | 24.02.2015 | 400[mg/m²/d] |
| 18 | Immunoadsorbtion | Single dose | 13.02.2015 | -- |
| 19 | Immunoadsorbtion | Single dose | 11.02.2015 | -- |
| 20 | Plasmapheresis | Single dose | 09.02.2015 | -- |

Edit

# Interim data report

| **Patient characteristics** | **n = 290** |
|---|---|
| Age, years (mean ± SD) | **10.7 ± 5.51** |
| Gender (female) | **114** (39.3%) |
| HLA-Mismatches (mean ± SD)<br>A<br>B<br>DR | <br>**0.87** ± 0.67<br>**1.13** ± 0.65<br>**0.93** ± 0.67 |
| Re-transplant, n (%) | **39** (13.4%) |
| Living donation, n (%) | **88** (30.3%) |
| Pre-emptive donation, n (%) | **75** (25.9%) |
| Donor age, years (mean ± SD) | **30.2** ± 16.9 |
| Delayed graft function, n (%) | **14** (4.8%) |
| Cold ischemia time, h (median, IQR) | **10.1** (3.0 – 15.0) |

# Interim data report

| **DSA** (based on "accepted visits") | 2016 | 2018 |
|---|---|---|
| Documented HLA-DSA measurements | **566** | **1469** |
| HLA-DSA negative | | 986 (67.1%) |
| DSA HLA-Class I positive (only) | | 36 (2.5%) |
| DSA HLA-Class II positive (only) | | 199 (13.5%) |
| DSA HLA-Class I & II positive | | 243 (16.3%) |
| Measurements per patient, median (IQR) | 5 (3 to 7) | 5 (2 to 8) |

# Interim data report: biopsies

| **Biopsy results** | n=147<br>2016 | **n=469**<br>2018 |
|---|---|---|
| Protocol biopsies | | 192 |
| Indication biopsies | | 277 |
| | | |
| Borderline | | **128** (27.3%) |
| BANFF IA to III | 12% | **55** (11.7%) |
| Acute ABMR | 3,4% | **36** (7.7%) |
| Chronic ABMR | 5.4% | **22** (4.7%) |
| IFTA I | 27% | **128** (27.3%) |
| IFTA II | 10% | **41** (8.7%) |
| C4d Positivity | 14% | **46** (9.8%) |

# Ongoing registry analyses

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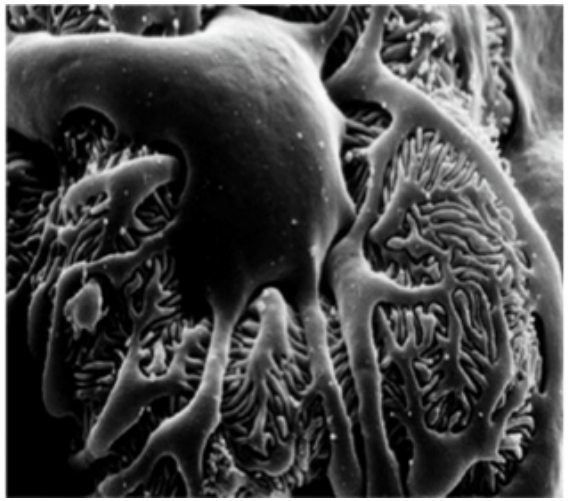
Emma Children's Hospital
Amsterdam UMC

# Incidence, treatment and outcome of recurrent steroid resistant nephrotic syndrome after pediatric kidney transplantation in Europe.

## CERTAIN Research Project

Antonia Bouts, Floor Veltkamp, Marina Vivarelli, Burkhard Tönshoff



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# BACKGROUND

**Responses of ESPN Survey on FSGS recurrence performed with working group "Transplantation" and "INS".**

**(20 Questions)**

- Total 807 children with focal segmental glomerulosclerosis
- 59 respondents
- 31 countries
- Frequency 0.12-3.82 / year
- 240 (30%) recurrence post-tx

Global insight into the variation of current practice of the treatment of FSGS
and its recurrence after transplantation.

# Certain research project: objectives

- To analyze the recurrence rate of nephrotic syndrome after kidney transplantation in children with steroid resistant nephrotic syndrome (SRNS).
- To analyze factors that predispose to post-transplantation recurrence of nephrotic syndrome.
- To investigate the relationship of biopsy results in the native kidneys of children with SRNS with outcome after kidney transplantation.
- To investigate the genetic mutation analysis and outcome of SRNS and recurrence after transplantation.
- To analyze differences in treatment policies of SRNS recurrence and outcome.
- To develop a European guideline for treatment of SRNS recurrence.

# Methods

- Retrospective analysis in Certain registry of all transplanted children with steroid resistant nephrotic syndrome.

- Using a minimal and study-specific data set in CERTAIN.
- Collecting and (re)appraisal of renal biopsy results of native kidney.
- Collecting genetic mutation analysis.

- (Future planning: Biobanking, mutation analysis of all patients, renal biopsy digital slides)

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1. The CERTAIN Registry
2. Ongoing projects
3. **Outlook: nephropathology module**

# What do we have so far?

- The CERTAIN Registry fills a gap in Europe for collaborative research and quality assurance in the field of paediatric renal transplantation.
- It is a comprehensive and flexible registry which serves to investigate cutting-edge research topics and allows an in-depth characterisation of specific patient cohorts.
- Data of more than 2,000 well-characterized patients with almost 21,000 study visits and more than 2,000 renal transplant biopsies have been already included.
- The mandatory minimal data set contains a data sheet on histopathological results.
- An extended pathology data set has been already implemented and is currently used for the ABMR study.
- An upload tool for pathology reports has been implemented in the registry.
- Technical prerequisites exist for an extended nephopathology tool.

Received: 5 November 2017 | Revised: 6 December 2017 | Accepted: 7 December 2017
DOI: 10.1111/ajt.14625

MEETING REPORT

AJT

# The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials

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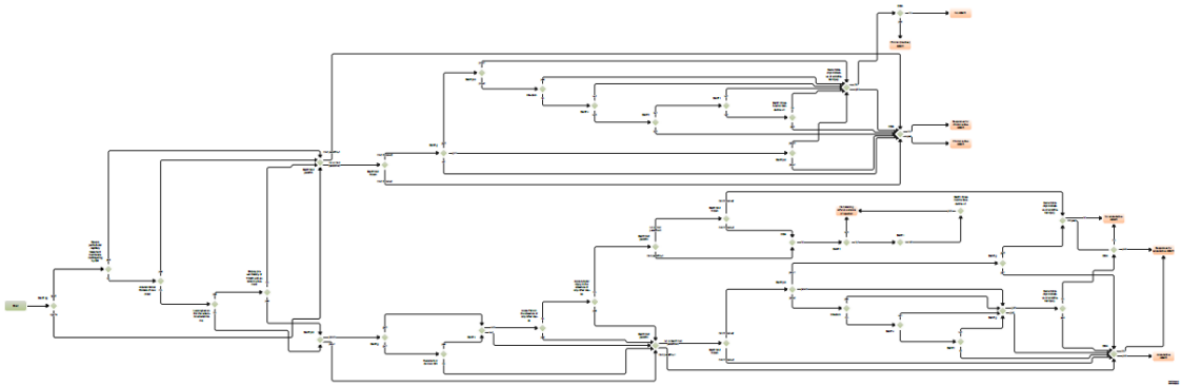
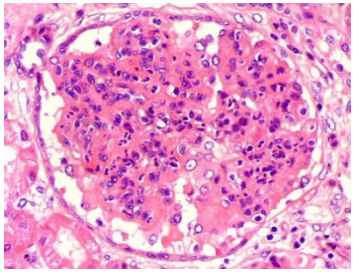
"…To this end, the Banff group formed a new working group on surrogate endpoints aimed at fostering collaboration with other professional societies and regulatory agencies on the common goal to develop a path forward to successful next generation multicenter trials and approval of novel drugs in solid organ transplantation…"

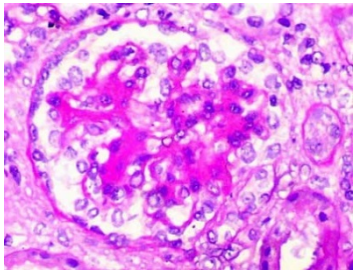
| | | | |
|---|---|---|---|
| Banff rules and dissemination (new working group) | J. U. Becker, C. Roufosse | Collation of contents of previous Banff reports in a central web-based, updatable repository including diagnostic parameters, definitions and rules.<br>Elaboration of a minimum dataset and algorithms for application of Banff classification. | Finalisation of the collation of current content during a meeting in London, UK in September 2017.<br>Preparation of a review manuscript with contents of previous Banff reports up to 2015.<br>Incorporation of possible changes in Banff 2017 report to content for the web-based repository in 2018. |

# Next steps: nephropathology module

1. Implementation of nephropathology module in CERTAIN Registry
2. Upload of slide scans (digital pathology)
3. Computerised image pathology (machine learning)

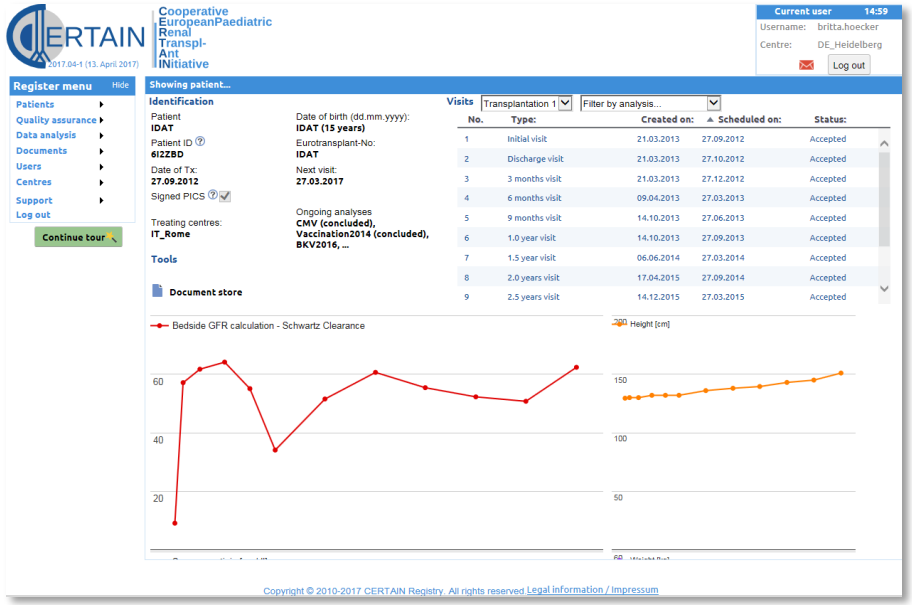






# Thank you for your attention!


**www.certain-registry.eu**



**40th Symposium**

Interdisciplinary Study Group „Renal Transplantation in Paediatrics“

**Online registration:**
**www.certain-registry.eu**

December 7 - 8, 2018

Crowne Plaza Hotel, Heidelberg, Germany

european society for paediatric nephrology

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

European Reference Network for rare or low prevalence complex diseases

Network Kidney Diseases (ERKNet)

# CERTAIN analysis protocol Template

| CERTAIN analysis protocol | |
|---|---|
| Study Title: | The title of the protocol should include study design, indication and, where applicable, dosage, dosage form, and comparative agent(s). |
| Institution Name | |
| Investigator Contact Information:<br>– Full address<br>– Phone No.<br>– Fax No.<br>– e-mail address | |

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

| | |
|---|---|
| 1. Objectives & Hypotheses | 1.1 List the objectives.<br><br>The objectives must clearly define and specifically state what the study is intended to accomplish, for example one primary efficacy objective.<br><br>One to two secondary objectives may be stated. They should be in the order of priority. The higher priority secondary objectives should have corresponding secondary hypotheses associated with them. Not all secondary objectives need to have a corresponding secondary hypothesis.<br><br>1.1.1 List the clinical hypotheses.<br><br>The primary efficacy and safety hypotheses should correspond directly with the primary objectives of the study. All hypotheses should be in the order of priority. If the study is estimation study, no hypotheses is needed. |
| 2. Background & Rationale, Significance of Selected Topic & Preliminary Data | A brief presentation should be made of the reasons for conducting the clinical study based on current knowledge of the product and/or disease state so that the study is presented in the proper perspective. Include the rationale for conducting the study and selecting the dose(s). Selected literature references critical to the study design, dosage selection, or rationale for the study should be cited, as appropriate. |
| 3. Study Design | This section is a concise overview of the study design stating the type of experimental design (observational or interventional; randomized block, crossover, etc.); whether the study is controlled (treatments other than the test product and/or placebo); whether the study is open or blinded/masked (single blind or double blind); the number of study centers (single or multicenter). The total number of patients included in the study and how they will be assigned to treatment groups must be indicated. When appropriate, state if the patients will be stratified. The procedures must be clear and concise. A description of the specific patient population to be studied should be stated. Both inclusion and exclusion criteria should be listed and should be consistent with the current product label.<br><br>If the study is intended to be observational then the protocol needs to state this and the expectations are different since most observational studies are database studies, retrospective, aggregate studies as opposed to open label studies for efficacy and safety. |
| 4. Study Flowchart | A study flow chart is highly recommended. It should display all clinical and laboratory measurements and the time periods (e.g., hours, days, weeks) at which data are to be collected. |
| 5. Study Procedures | This section is a detailed explanation of the experimental design. The use of subheadings, lists, tables, or outlines are recommended. Describe the initial screening period(s), baseline period(s), treatments to be compared, study configuration (parallel, crossover, etc.), duration of the treatment period(s), control group(s), follow-up procedures, and length of time specified for washout intervals and safety follow-up. In protocols that specify a screening or washout period, indicate that once a patient signs a consent form, a unique number (screening or baseline number) should be assigned for identification purposes. It should be noted that that under no circumstances should a patient be assigned more than one allocation number |
| 6. Study Duration | Estimate the length of time (e.g., number of days, weeks, months) required to recruit patients and complete the study. |



# CERTAIN analysis protocol

- Objectives/hypotheses
- Background/rationale
- Study design
- Study flowchart
- Study procedures
- Study duration

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

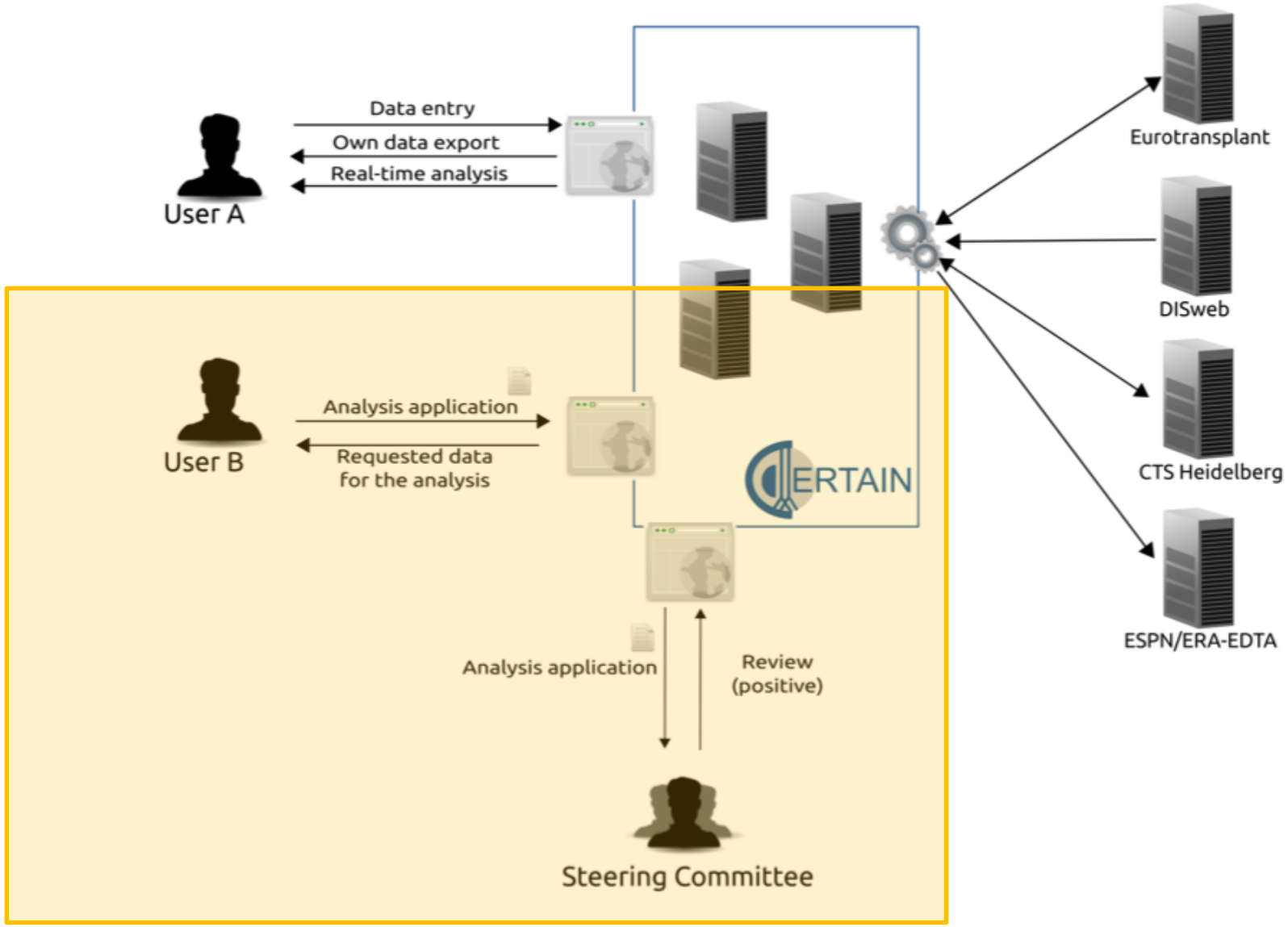
| | |
|---|---|
| 7. Statistical Analysis and Sample Size Justification | State who will be responsible for analyzing the study data (Investigator, contract CRO, etc.). When appropriate state how the blind will be maintained during the study, as appropriate, and when the data will be unblinded. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete.<br><br>Variables/Time Points of Interest<br><br>All variables (primary and secondary) that are listed in the study hypotheses, and the time points at which they will be analyzed, need to be described in detail.<br><br>Efficacy variables discussed in this section should have been included as part of an objective or hypothesis section. These variables and the time points at which they are to be analyzed should be consistent with the primary and secondary hypotheses, i.e., primary variables and time points should relate to the primary hypotheses.<br><br>Statistical Methods<br><br>All planned primary analyses and key secondary analyses should be discussed in this section. If other secondary and tertiary analyses are planned, then a statement should be included in this section as to what these analyses are.<br><br>Describe in detail the statistical methods that will be used for the primary hypotheses or estimation. State the statistical tests which will be used (e.g., ANOVA, Kaplan-Meier) along with other important considerations (e.g., factors in ANOVA, pre-specification of covariates, strata for Mantel-Haenszel, use of historical controls).<br><br>Multiplicity<br><br>If appropriate, describe the multiplicity approach to support the statistical conclusions of the trial.<br><br>Power/Sample Size:<br><br>In studies with hypotheses, minimally, for the primary endpoint of the study, a power statement needs to be included to show the detectable difference relative to the primary hypothesis. For example, the following level of detail is expected:<br><br>Based upon a sample size of n=40 patients per group, this study has 80% power to detect a 5.4 mmHg difference between groups in systolic blood pressure; this calculation is based on a between subject standard deviation of change of 9 mmHg for systolic BP (reference for where this variability statement originated).<br><br>In estimation studies, the precision of the primary/secondary estimations needs to be given with the sample size of the trial. |
| 8. References | All literature references cited in the protocol should be listed accordingly in the reference section. |



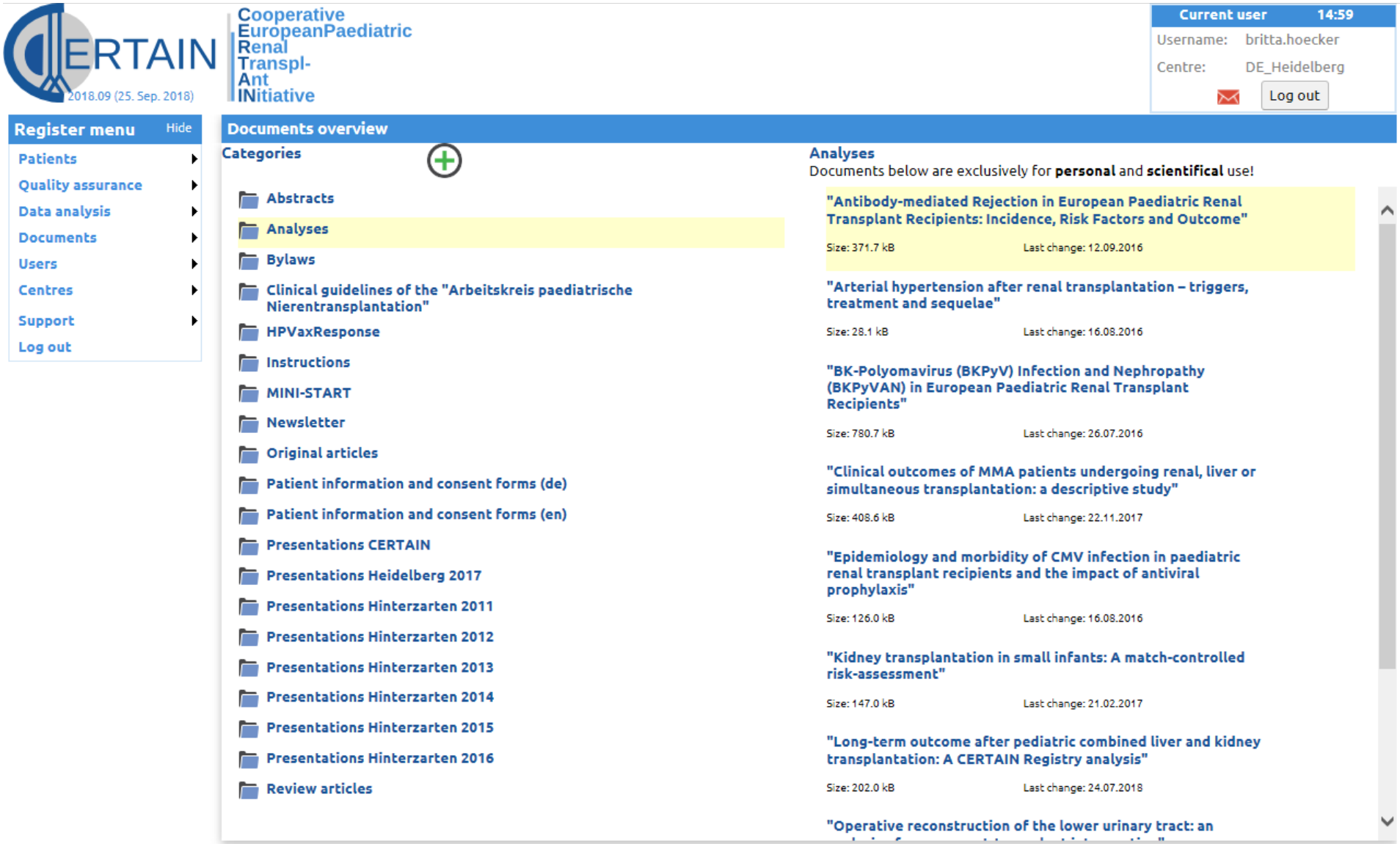
# CERTAIN analysis protocol

- Variables/time points
- Statistical methods
- Sample size
- References

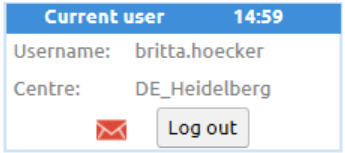
# Steering committee

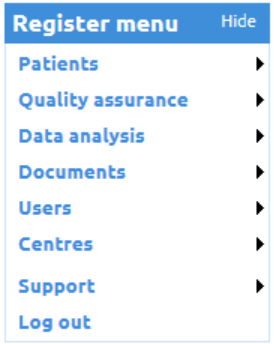


# Analyses



# Documents

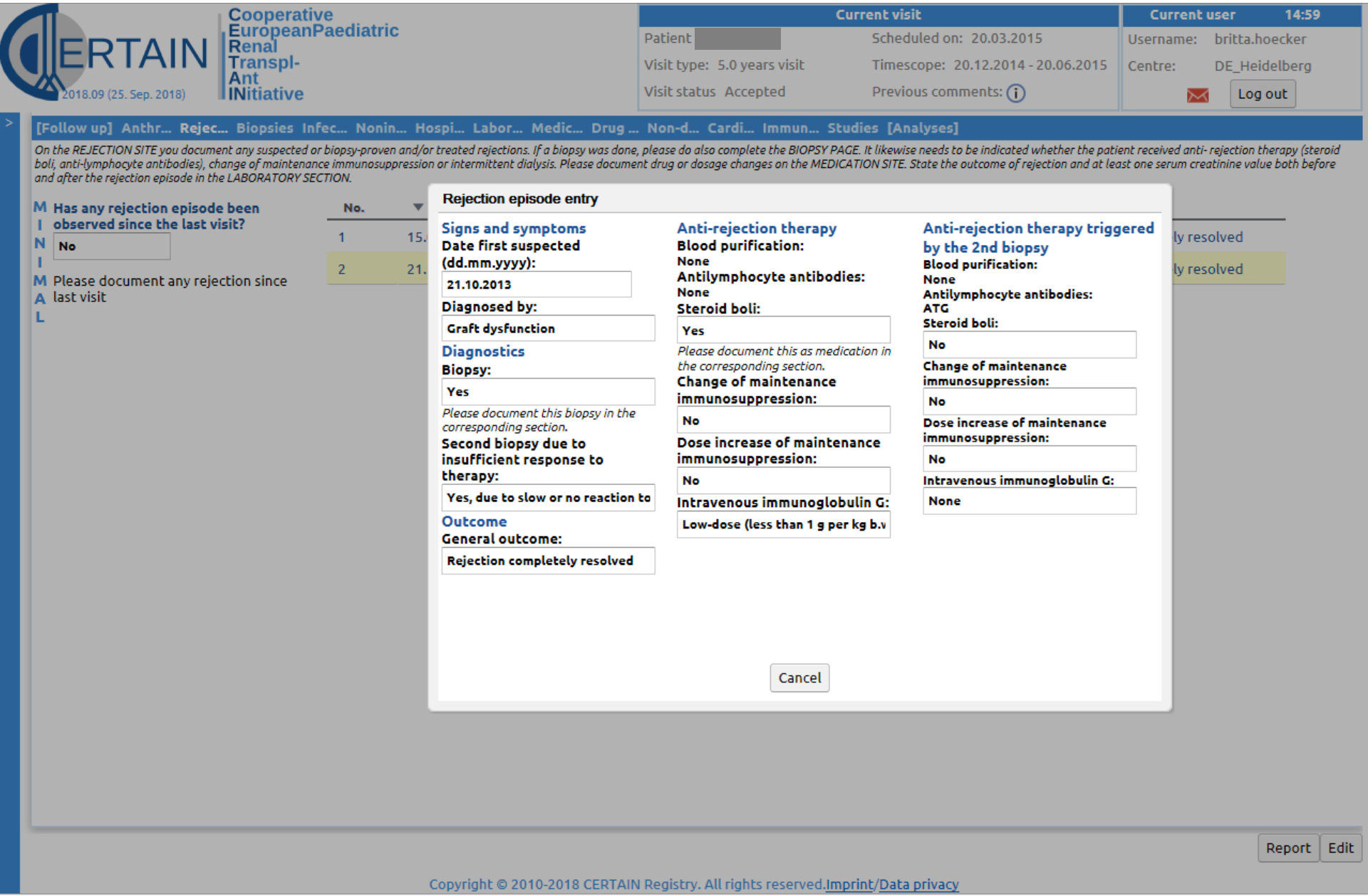




**Documents overview**

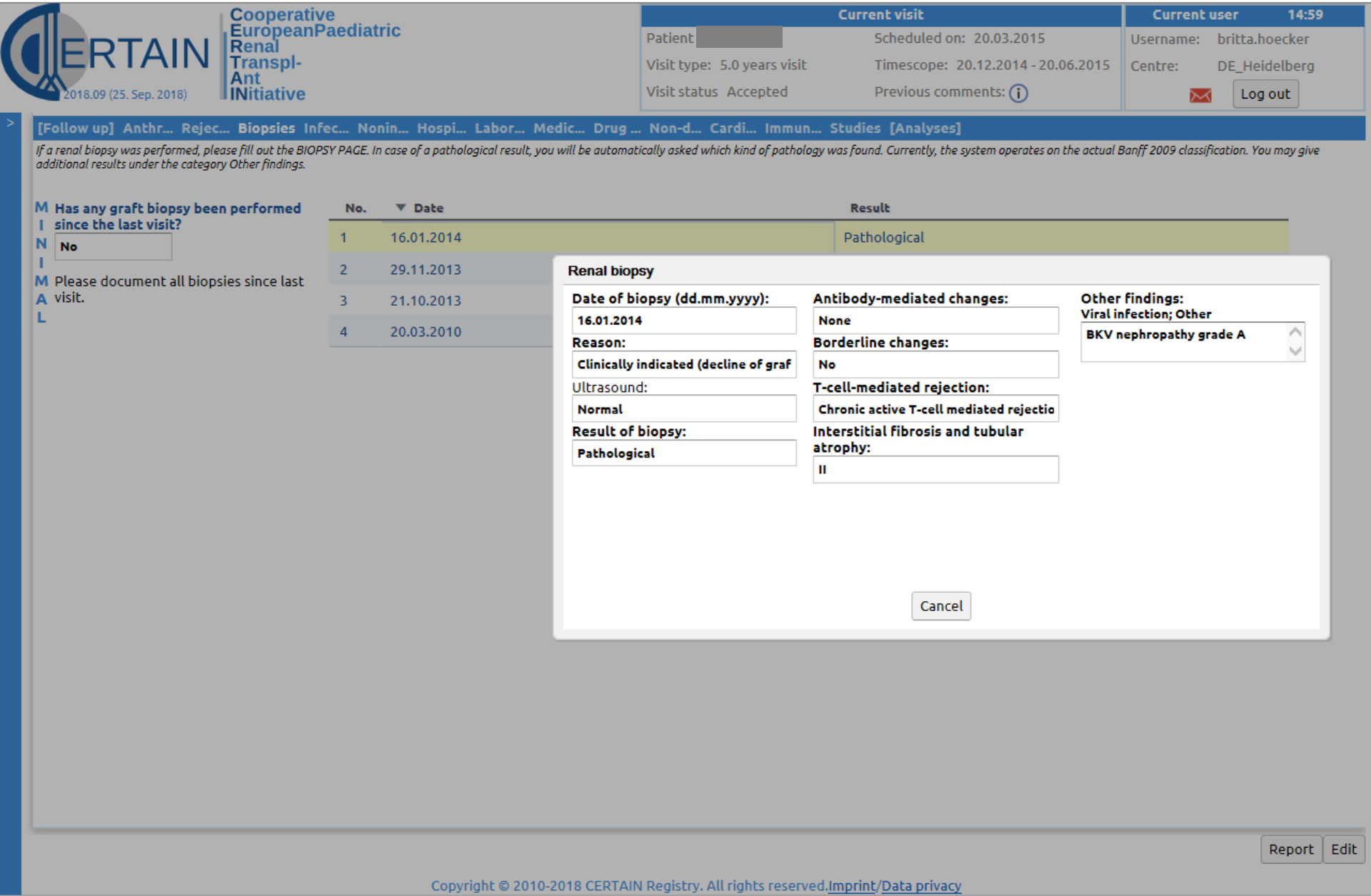
**Categories**

- Abstracts
- Analyses
- Bylaws
- Clinical guidelines of the "Arbeitskreis paediatrische Nierentransplantation"
- HPVaxResponse
- Instructions
- MINI-START
- Newsletter
- Original articles
- Patient information and consent forms (de)
- Patient information and consent forms (en)
- Presentations CERTAIN
- Presentations Heidelberg 2017
- Presentations Hinterzarten 2011
- Presentations Hinterzarten 2012
- Presentations Hinterzarten 2013
- Presentations Hinterzarten 2014
- Presentations Hinterzarten 2015
- Presentations Hinterzarten 2016
- Review articles

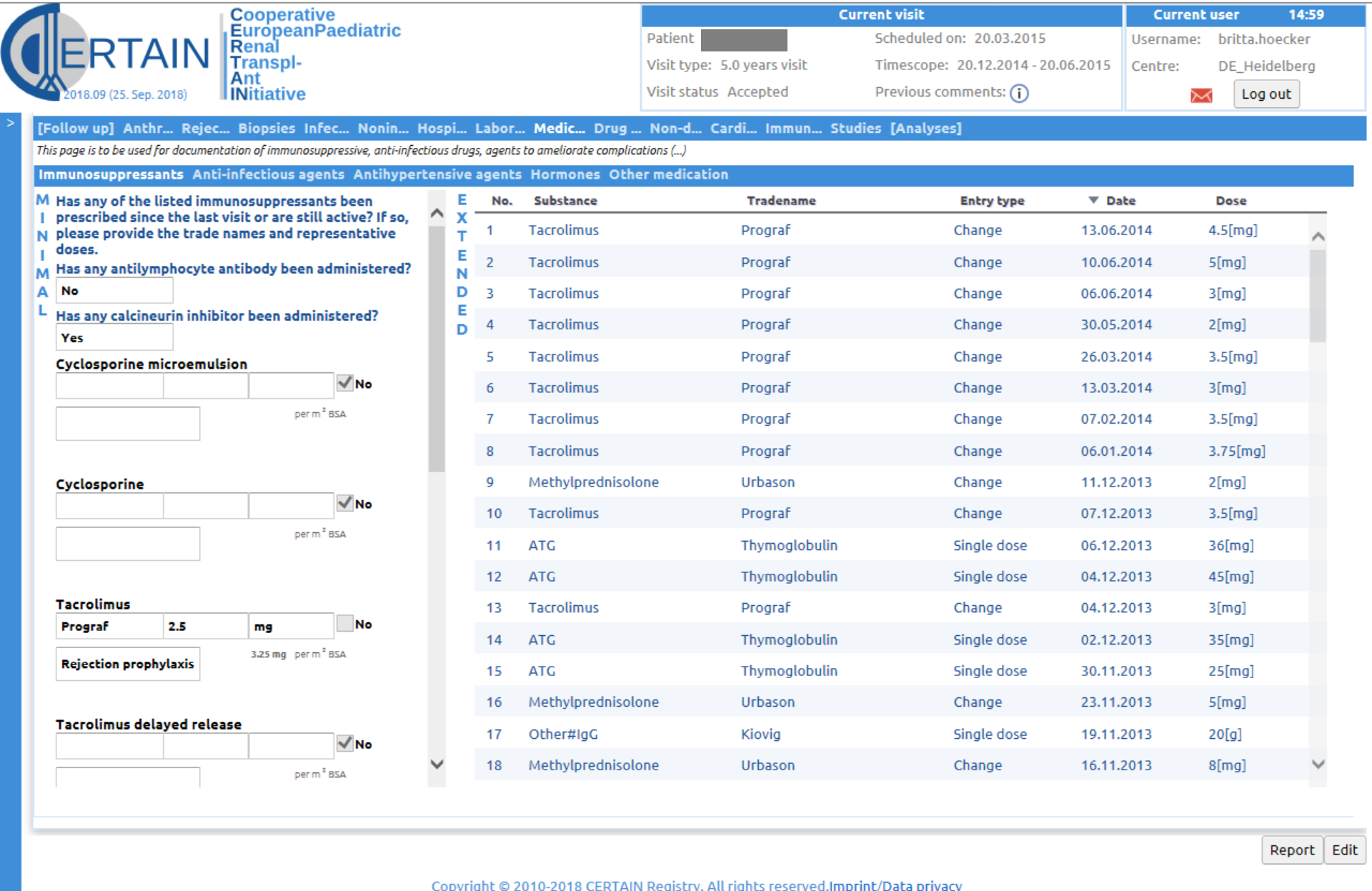
# Graft rejection



# Biopsy


CERTAIN
Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative
2018.09 (25. Sep. 2018)
Current visit
Patient
Scheduled on: 20.03.2015
Visit type: 5.0 years visit
Timescope: 20.12.2014 - 20.06.2015
Visit status Accepted
Previous comments:
Current user 14:59
Username: britta.hoecker
Centre: DE_Heidelberg
Log out
[Follow up] Anthr... Rejec... Biopsies Infec... Nonin... Hospi... Labor... Medic... Drug ... Non-d... Cardi... Immun... Studies [Analyses]
If a renal biopsy was performed, please fill out the BIOPSY PAGE. In case of a pathological result, you will be automatically asked which kind of pathology was found. Currently, the system operates on the actual Banff 2009 classification. You may give additional results under the category Other findings.
MINIMAL
Has any graft biopsy been performed since the last visit?
No
Please document all biopsies since last visit.
No.
Date
Result
1 16.01.2014 Pathological
2 29.11.2013
3 21.10.2013
4 20.03.2010
Renal biopsy
Date of biopsy (dd.mm.yyyy):
16.01.2014
Reason:
Clinically indicated (decline of graf
Ultrasound:
Normal
Result of biopsy:
Pathological
Antibody-mediated changes:
None
Borderline changes:
No
T-cell-mediated rejection:
Chronic active T-cell mediated rejectio
Interstitial fibrosis and tubular atrophy:
II
Other findings:
Viral infection; Other
BKV nephropathy grade A
Cancel
Report
Edit
Copyright © 2010-2018 CERTAIN Registry. All rights reserved.Imprint/Data privacy

# Immunosuppression



# Non-infectious complications

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative
2018.09 (25. Sep. 2018)

| Current visit | | Current user | 14:59 |
|---|---|---|---|
| Patient [redacted] | Scheduled on: 20.03.2015 | Username: | britta.hoecker |
| Visit type: 5.0 years visit | Timescope: 20.12.2014 - 20.06.2015 | Centre: | DE_Heidelberg |
| Visit status Accepted | Previous comments: | | Log out |

[Follow up] Anthr... Rejec... Biopsies Infec... **Nonin...** Hospi... Labor... Medic... Drug ... Non-d... Cardi... Immun... Studies [Analyses]

*Please indicate all relevant transplant-related complications that patients suffered, except infections. The latter are to be documented (...)"*

MINIMAL

**Has any of the listed complications been observed since the last visit?**

| | |
|---|---|
| Arterial hypertension | Yes |
| Left ventricular hypertrophy | No |
| Diabetes mellitus | No |
| Anorexia | No |
| Cushingoid habitus | No |
| Growth impairment | No |
| Tumour | No |
| Fracture | No |
| Upper gastrointestinal compl. | No |
| Lower gastrointestinal compl. | No |
| Glaucoma | No |
| Cataract | No |
| Papilloedema | No |
| Fundus hypertonicus | No |
| Gingival hyperplasia | No |
| Hypertrichosis | No |
| Striae | No |
| Skin warts | No |
| Acne | No |

| No. | Date | Type | Immunosuppression changed | End date |
|---|---|---|---|---|
| 1 | 30.09.2013 | Upper gastrointestinal | Yes | 14.10.2013 |
| 2 | 01.02.2013 | Upper gastrointestinal | No | 03.02.2013 |
| 3 | 09.11.2012 | Leukocytopaenia | Yes | 15.11.2012 |
| 4 | 18.07.2011 | Lower gastrointestinal | No | 14.08.2011 |
| 5 | 23.05.2011 | Lower gastrointestinal | Yes | 16.06.2011 |
| 6 | 28.09.2010 | Secondary hyperparathyroidism | No | -- |
| 7 | 20.09.2010 | Anaemia | No | 24.02.2011 |
| 8 | 09.09.2010 | Leukocytopaenia | Yes | 12.12.2010 |
| 9 | 04.04.2010 | Lower gastrointestinal | Yes | 07.04.2010 |
| 10 | 20.03.2010 | Arterial hypertension | No | -- |

Report Edit

# Initial recipient data

CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative
2018.09 (25. Sep. 2018)

| Current visit | | Current user 14:59 | |
|---|---|---|---|
| Patient [redacted] | Scheduled on: 20.03.2010 | Username: | britta.hoecker |
| Visit type: Initial visit | Timescope: 05.03.2010 - 04.04.2010 | Centre: | DE_Heidelberg |
| Visit status Accepted | Previous comments: | | Log out |

General History Donor **Recip...** Vacci... Vacci... Vacci... Patie... Psych... [Continuous entries] [Analyses]

*Here the requisite recipient- and surgery-related data should be entered. Again, some items may already have been documented by ET. If the patient participates in a prospective study, please fill in the page STUDIES under CONTINUOUS ENTRIES.*

MINIMAL

**Type of transplantation:**
Right donor kidney

**Cold ischaemia time (hours/minutes):**
24 | 0

**Warm ischaemia time (hours/minutes):**
8 | 0 Unknown

**Biopsy before/during transplantation:**
Yes

**Biopsy result:**
mm0, g0, ci1, ct1, cv0, partly necrosis of tubular epithelia

**Nephrectomy of native kidneys?**
No

**Explantation of previous kidney grafts?**
No

**Blood group:**
A

**ABO group incompatible transplantation:**
No

**CMV-IgG:**
Negative

**EBV-IgG:**
Negative

**HLA-A**

| | Broad | Split | Allele |
|---|---|---|---|
| 1 | A1 | | |
| 2 | blank | | |

**HLA-B**

| | Broad | Split | Allele |
|---|---|---|---|
| 1 | B8 | | |
| 2 | B17 | B57 | B*57:XX |

**HLA-DR**

| | Broad | Split | Allele |
|---|---|---|---|
| 1 | DR3 | | |
| 2 | DR7 | | |

**Current PRA (in %):**
0

**Highest PRA (in %):**
Unknown

**Desensitisation procedure:**
No

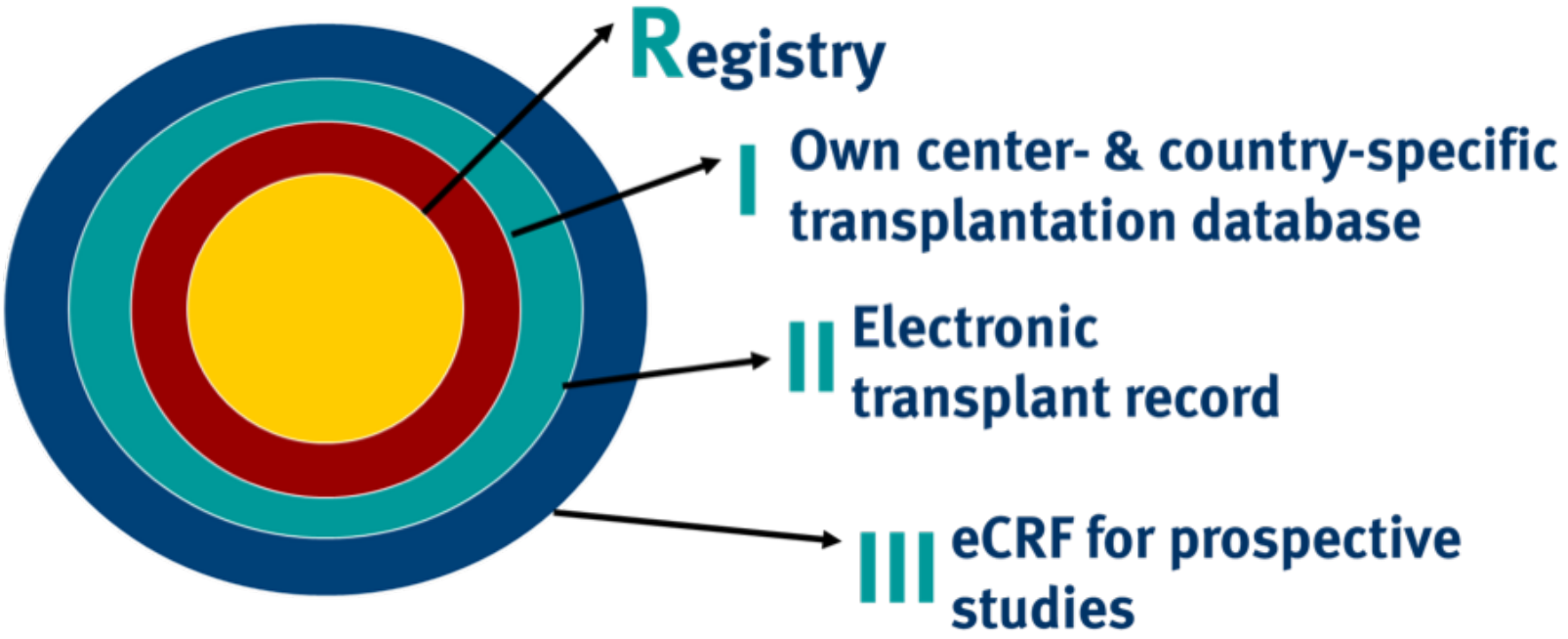
Edit

# The CERTAIN Registry: A Novel, Web-Based Registry and Research Platform for Pediatric Renal Transplantation in Europe

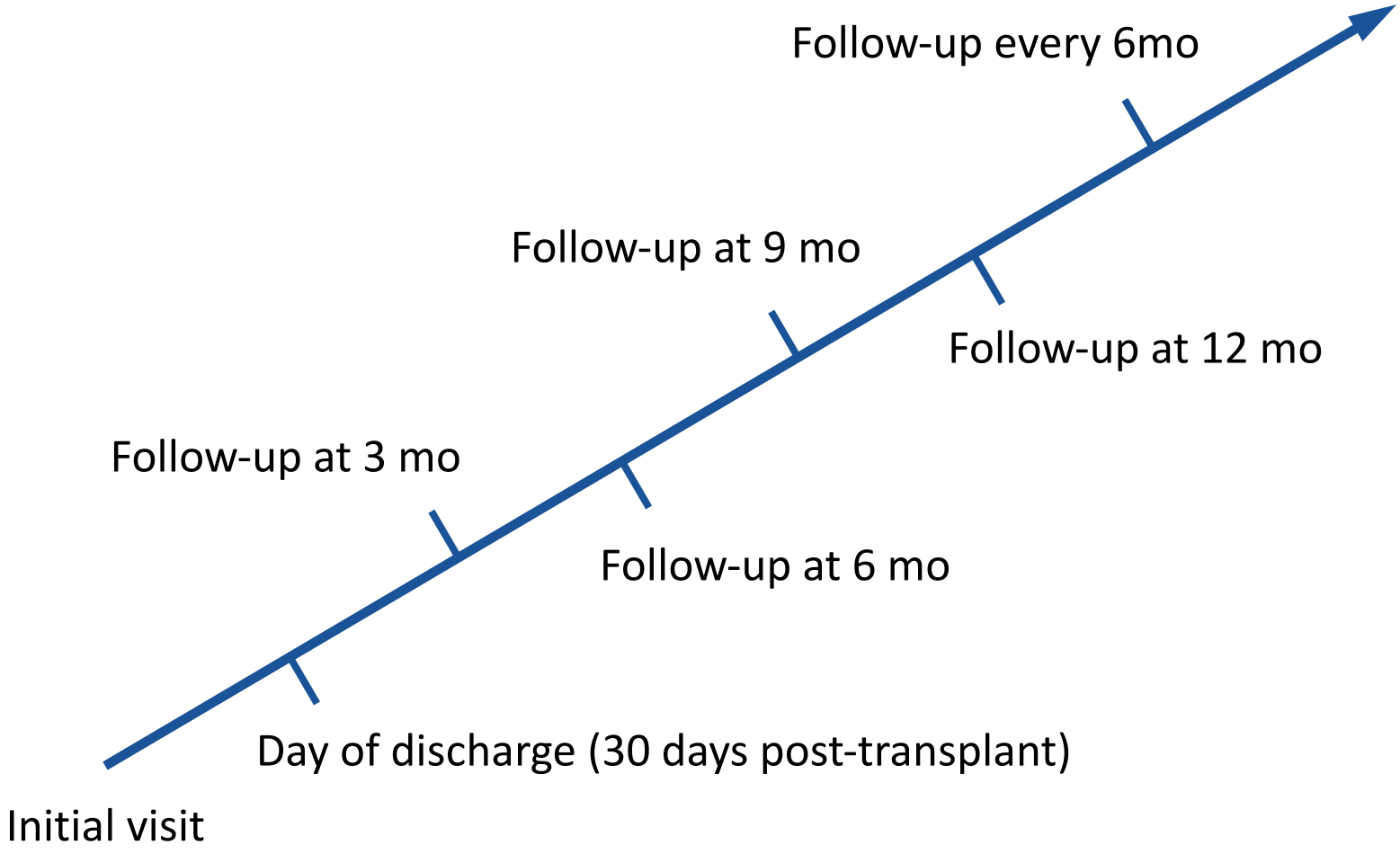
L. Plotnicki, C.D. Kohl, B. Höcker, K. Krupka, A. Rahmel, L. Pape, P. Hoyer, S.D. Marks, N.J.A. Webb, O. Söylemezoglu, R. Topaloglu, A.J. Szabo, T. Seeman, E.A. Marlies Cornelissen, N. Knops, R. Grenda, and B. Tönshoff

*Transplantation Proceedings,* 45, 1414–1417 (2013)

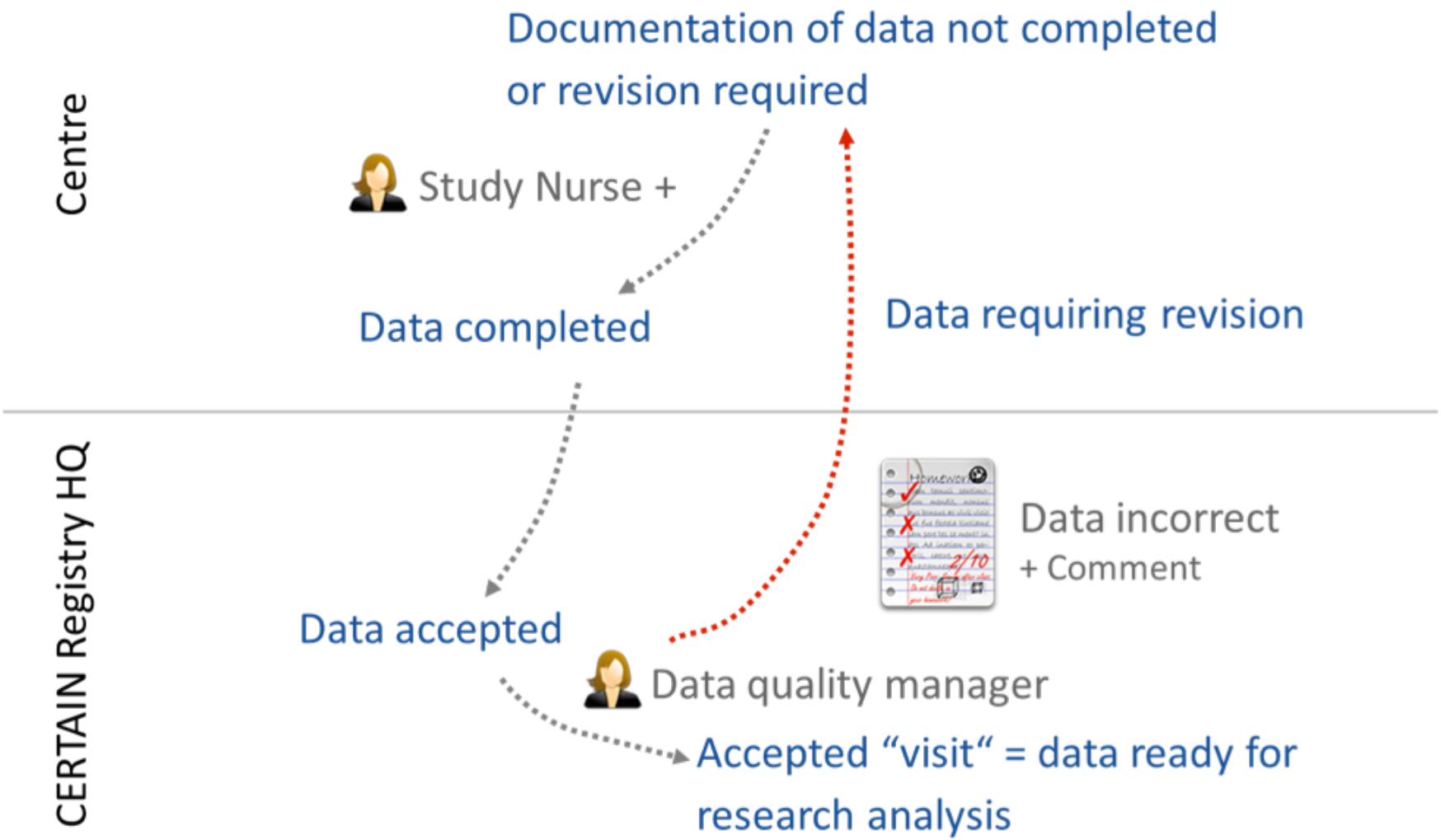
# Data volume & usage



# Data entry schedule

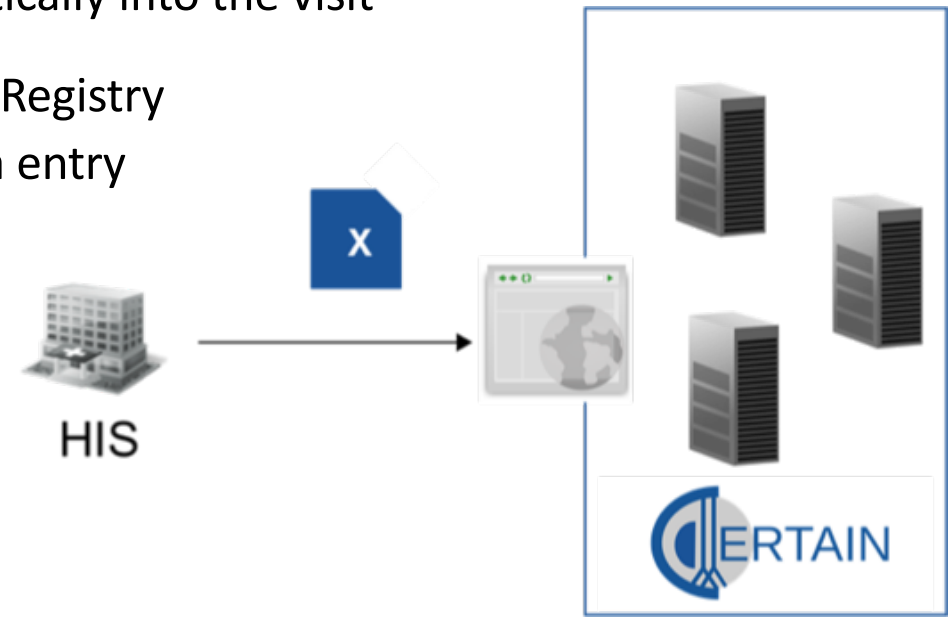


# Data quality assurance process



# Automatic data entry: import of laboratory values

- Activated for the centers in Germany (Essen, Heidelberg, Leipzig, Stuttgart), Hungary (Budapest), Italy (Rome), UK (Manchester) and Switzerland (Zürich)
- Steps for importing data
  - Export laboratory values as a standardized Excel file from the hospital information system (HIS)
  - Upload file to the CERTAIN Registry for a specific visit
  - Values get integrated automatically into the visit
- Benefits for both users and CERTAIN Registry
  - Reduced time for manual data entry
  - Improved data quality



# Centre report

## Report 10/2018

### All Centres

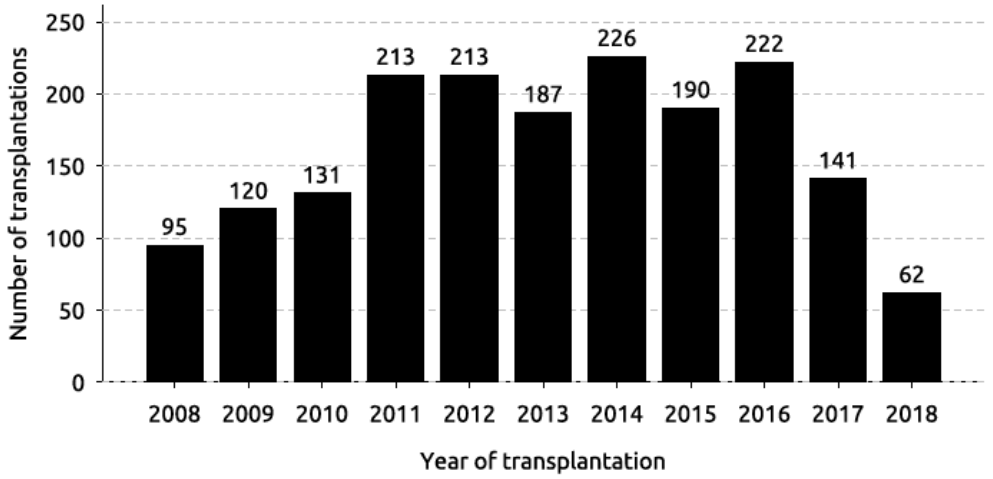
CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

## Registry

| | |
|---|---|
| Total number of patients: | 2212 |
| Total number of transplants: | 2265 |
| Total number of visits: | 20987 |

## Cohort

| | |
|---|---|
| Total number of patients: | 2212 |
| Total number of transplants: | 2265 |
| Total number of visits: | 20987 |
| Timeliness of follow-up: | 35.3% |




## Number of kidney transplantations (incl. living-related Tx)

| Year | No. of Tx reported by ET* | No. of Tx for which D/R data were requested from ET | No. of recipients in adult care |
|---|---|---|---|
| 2018 | 100 | 17 (17.0%) | 0 |
| 2017 | 138 | 53 (38.4%) | 2 |
| 2016 | 133 | 70 (52.6%) | 2 |

* up to recipient age of 21 years

# Centre report

## Centre Report 10/2018

### DE_Heidelberg

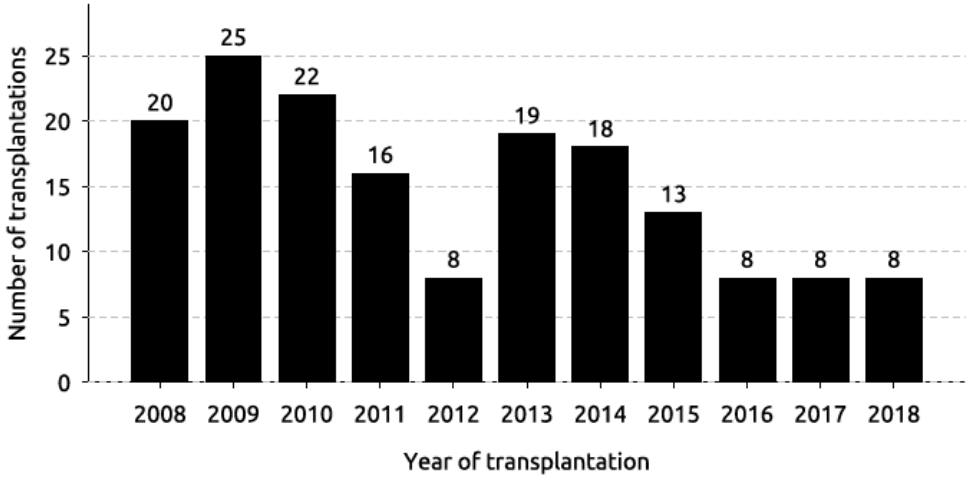
CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

### Registry

| | |
|---|---|
| Total number of patients: | 2212 |
| Total number of transplants: | 2265 |
| Total number of visits: | 20987 |

### Centre

| | |
|---|---|
| Total number of patients: | 349 |
| Total number of transplants: | 382 |
| Total number of visits: | 5669 |
| Timeliness of follow-up: | 50.0% |



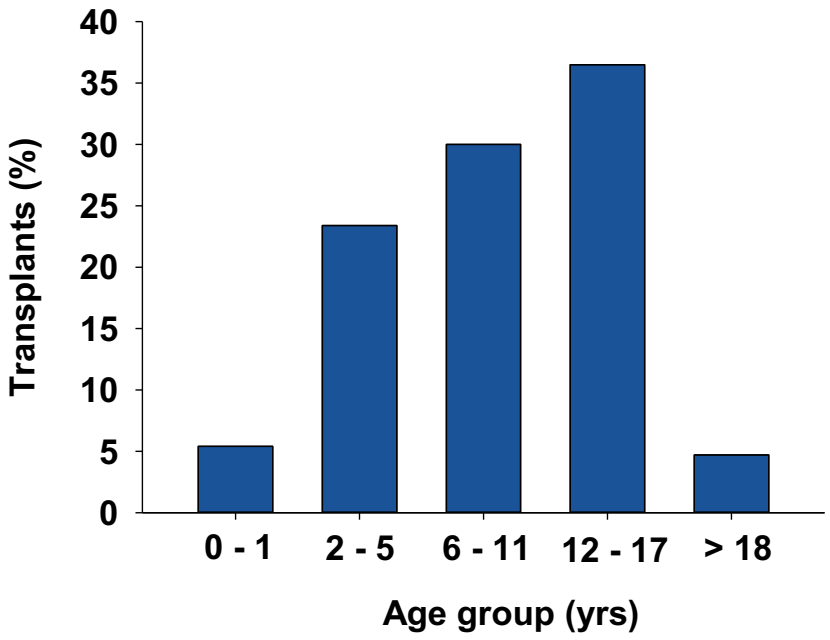

## Number of kidney transplantations (incl. living-related Tx)

| Year | No. of Tx reported by ET* | No. of Tx for which D/R data were requested from ET | No. of recipients in adult care |
|---|---|---|---|
| 2018 | 12 | 8 (66.7%) | 0 |
| 2017 | 12 | 8 (66.7%) | 1 |
| 2016 | 8 | 8 (100.0%) | 0 |

* up to recipient age of 21 years

# Recipient age and donor type

## Recipient age at RTx



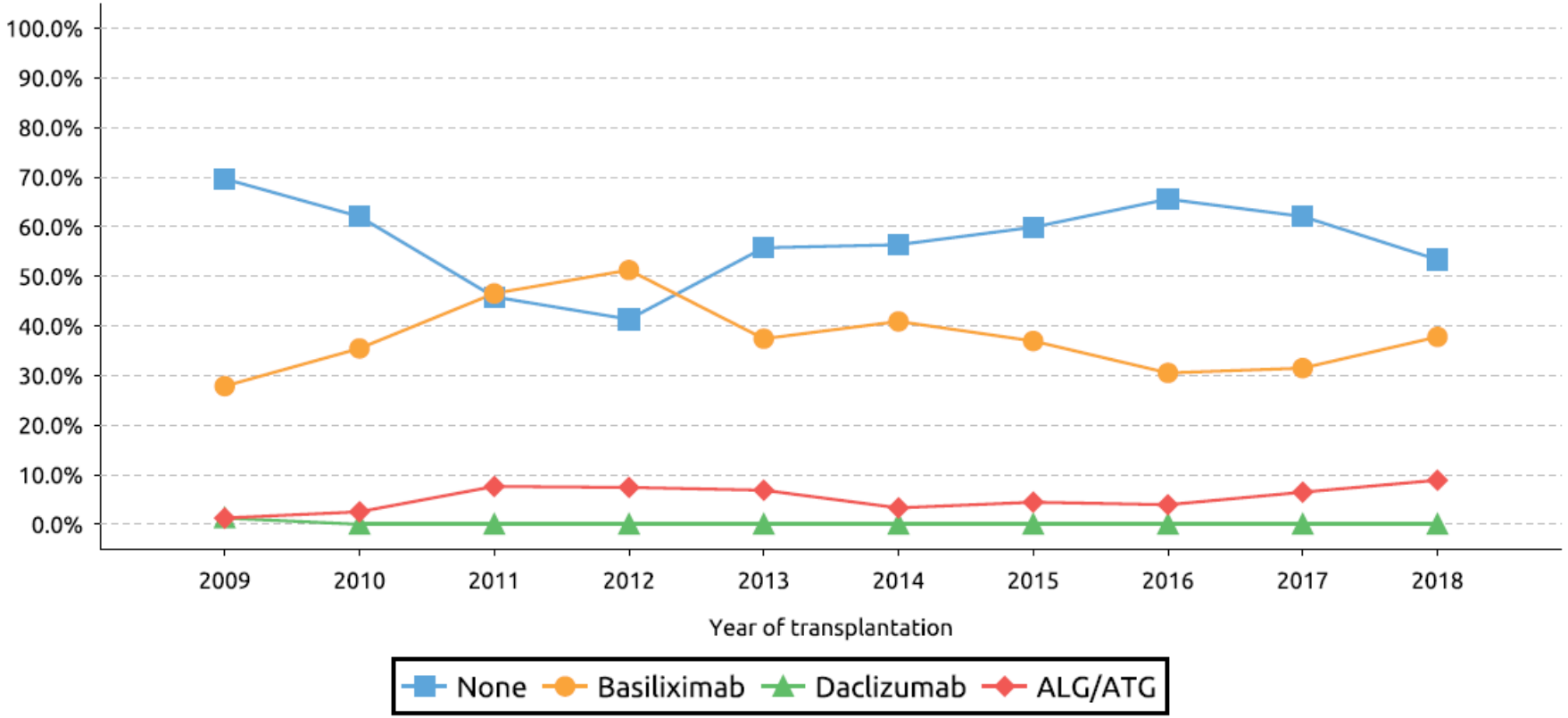

## Donor type


**n = 2265 transplants**

# Induction therapy

## Immunosuppressive regimen within the last 10 years (N=1222)

### Induction therapy stratified by substance



# Maintenance immunosuppressive treatment