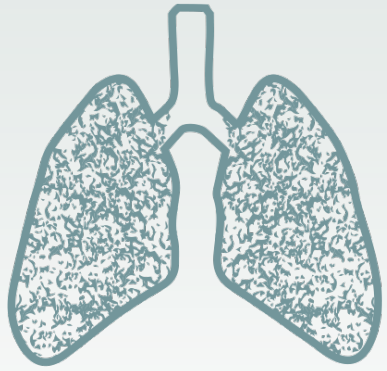


European Multipartner IPF Registry
9th international SC meeting

Martina Vašáková[1], Karel Hejduk[2]

[1] Thomayer Hospital, Prague, Czech Republic;

[2] Faculty of Medicine, Masaryk University

MUNI MED Institute of Biostatistics and Analyses

Project management team

Karel Hejduk

Senior PM

Jana Gregorová

Project manager

Ondřej Májek

Senior data analyst

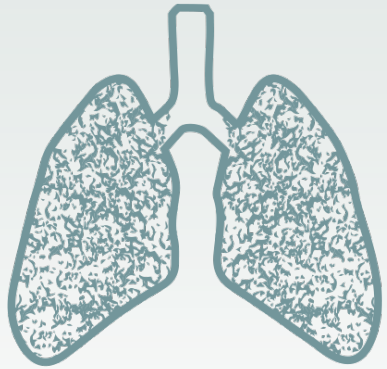
Jakub Gregor

Website, quality control

Lucie Martykánová

Economics, administration

EMPIRE
(IPF)



EMPIRE
(IPF)

Current state of the registry

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Representation of countries in the EMPIRE registry

11 countries, 51 centres

- **Czech Republic (17 centres)**
- **Hungary (6 centres)**
- **Poland (9 centres)**
- **Slovakia (6 centres)**
- **Serbia (4 centres)** (1 new centre)
- **Turkey (1 centre)**
- **Croatia (2 centres)** (1 terminated cooperation)
- **Israel (2 centres)** (1 new centre)
- **Bulgaria (1 centre)**
- **Austria (2 centres s)** (1 new centre)
- **Macedonia (1 centre)**

EMPIRE (IPF)

New countries/centres interested in participation

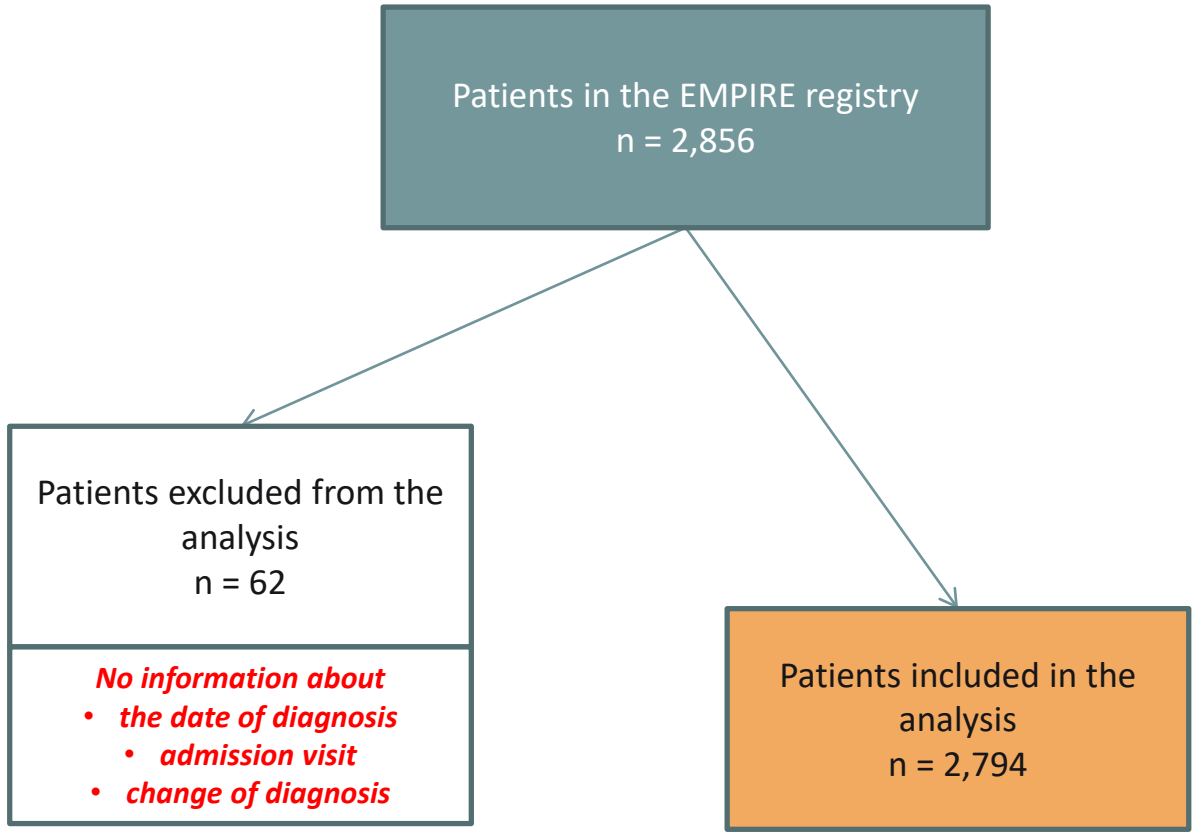
Country	Comment
Poland	1 new centre (Lublin) will join the registry (EC approval, contract sent)
Hungary	3 new centres wish to join the registry (EC approval, contract sent)
Romania	Negotiation with Irina Strambu about possibility to join the registry (5 centres, negotiation underway)
Latvia	Latvia would like to join EMPIRE (core information, documents sent to Alvils Krams)
Turkey	Centres from the Turkish Respiratory Society (contact from Prof. Jovanovic, negotiation underway)

EMPIRE (IPF)

Number of valid patients by countries in the EMPIRE registry

n = 2,794

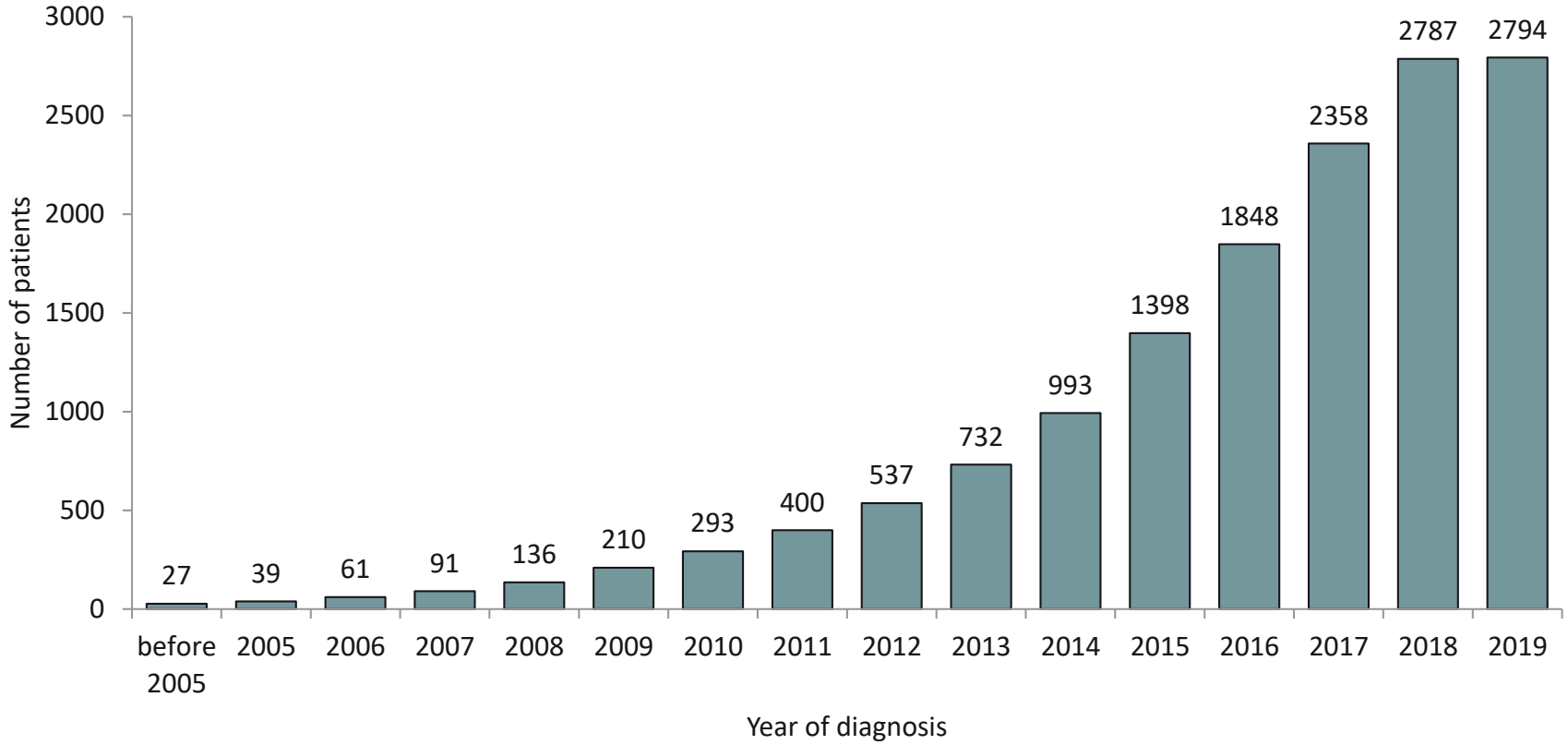
	Number of patients
Czech Republic	933 (33.4%)
Turkey	518 (18.5%)
Poland	496 (17.8%)
Hungary	245 (8.8%)
Slovakia	191 (6.8%)
Israel	150 (5.4%)
Serbia	107 (3.8%)
Croatia	81 (2.9%)
Austria	59 (2.1%)
Bulgaria	14 (0.5%)



EMPIRE (IPF)

Number of newly diagnosed patients

n = 2,794

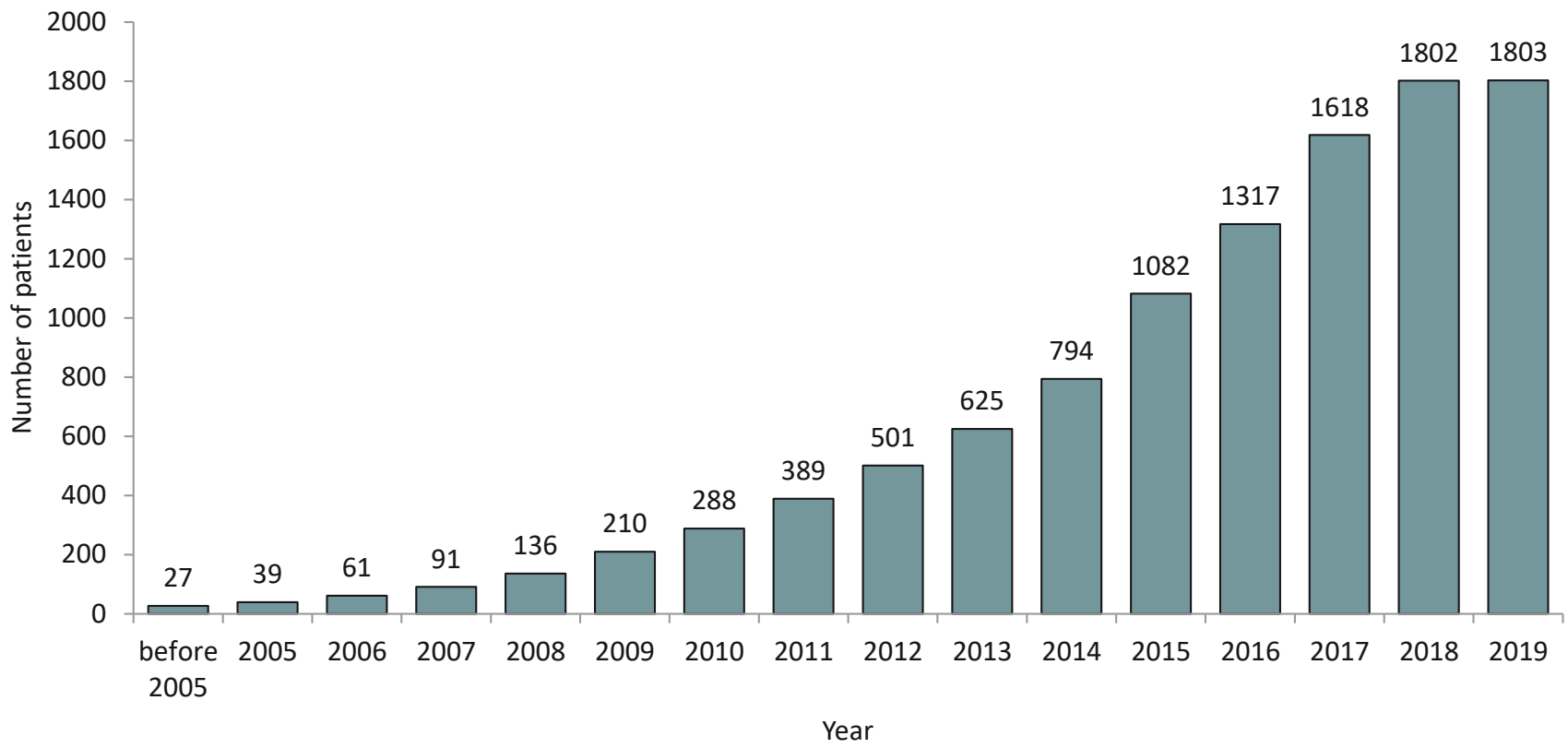


EMPIRE (IPF)

Number of monitored patients

n = 2,794

Year	Number of terminated follow-ups (with known date)
2010	5
2011	6
2012	25
2013	71
2014	92
2015	117
2016	215
2017	209
2018	245
2019	6
Total	991



The number of patients in the EMPIRE registry monitored in a given year is reduced by the number of patients with terminated follow-up due to death (n = 653), lung transplantation (n = 45), patients lost from follow-up (n = 272), other (n = 36). The date of death is unknown in 15 patients.

EMPIRE (IPF)

Contracts with centres

- **From April 2018 only contracts with the centres/hospitals are possible.**
- According to the new regulations that the Masaryk University has implemented and anticorruption law of the Czech Republic it is no longer possible to make direct agreements with data managers (investigators).
- Contract templates have been sent to all centres; the centres are obliged to pay the remuneration to the data managers.
- **Four reminders** have been sent to date; unfortunately **some centres have not responded** at all.
- Please try to remind it to the centres in your country. If the contracts are not signed, the registry will not work and we will not be able to send payments.

EMPIRE
(IPF)

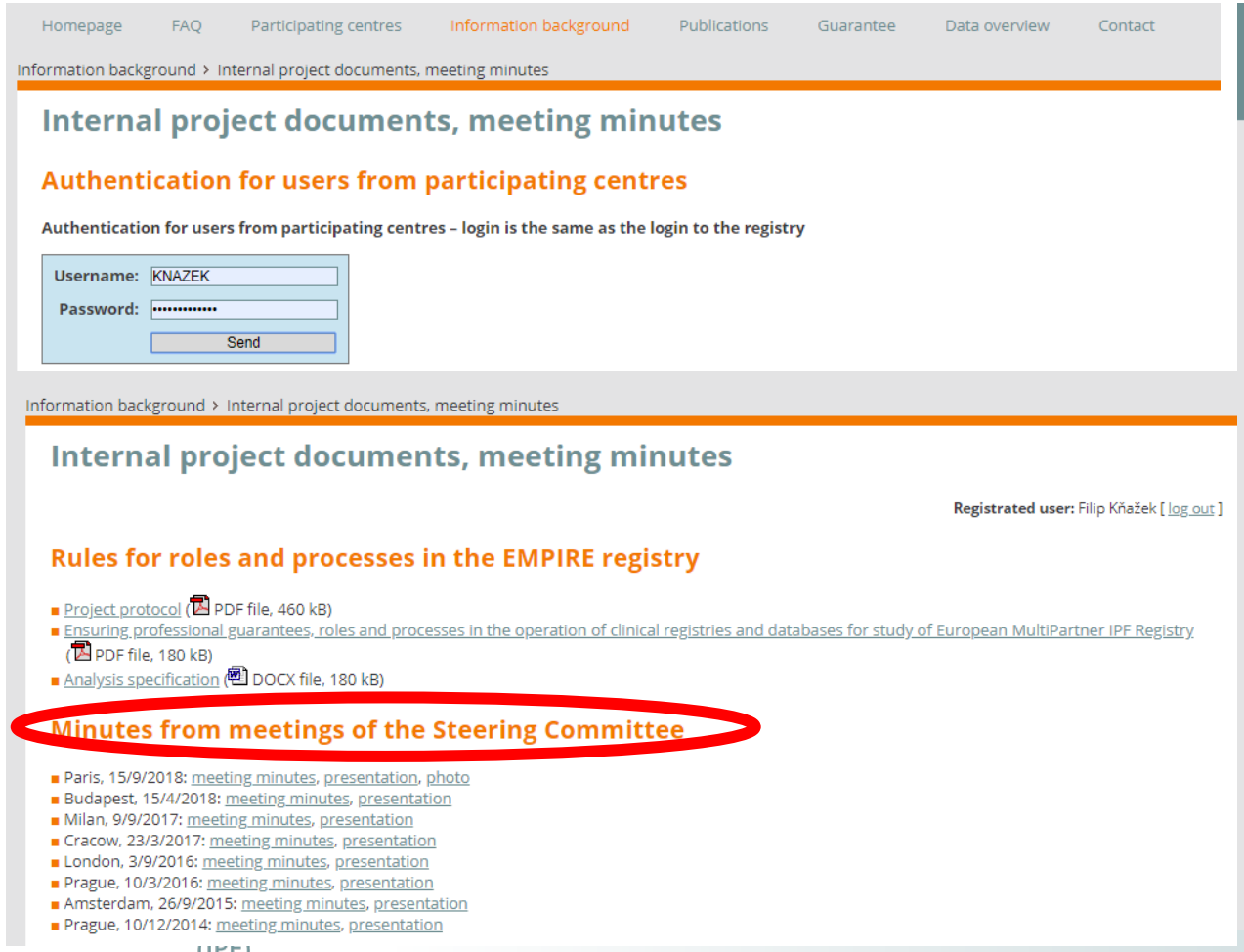
Overview of contracts

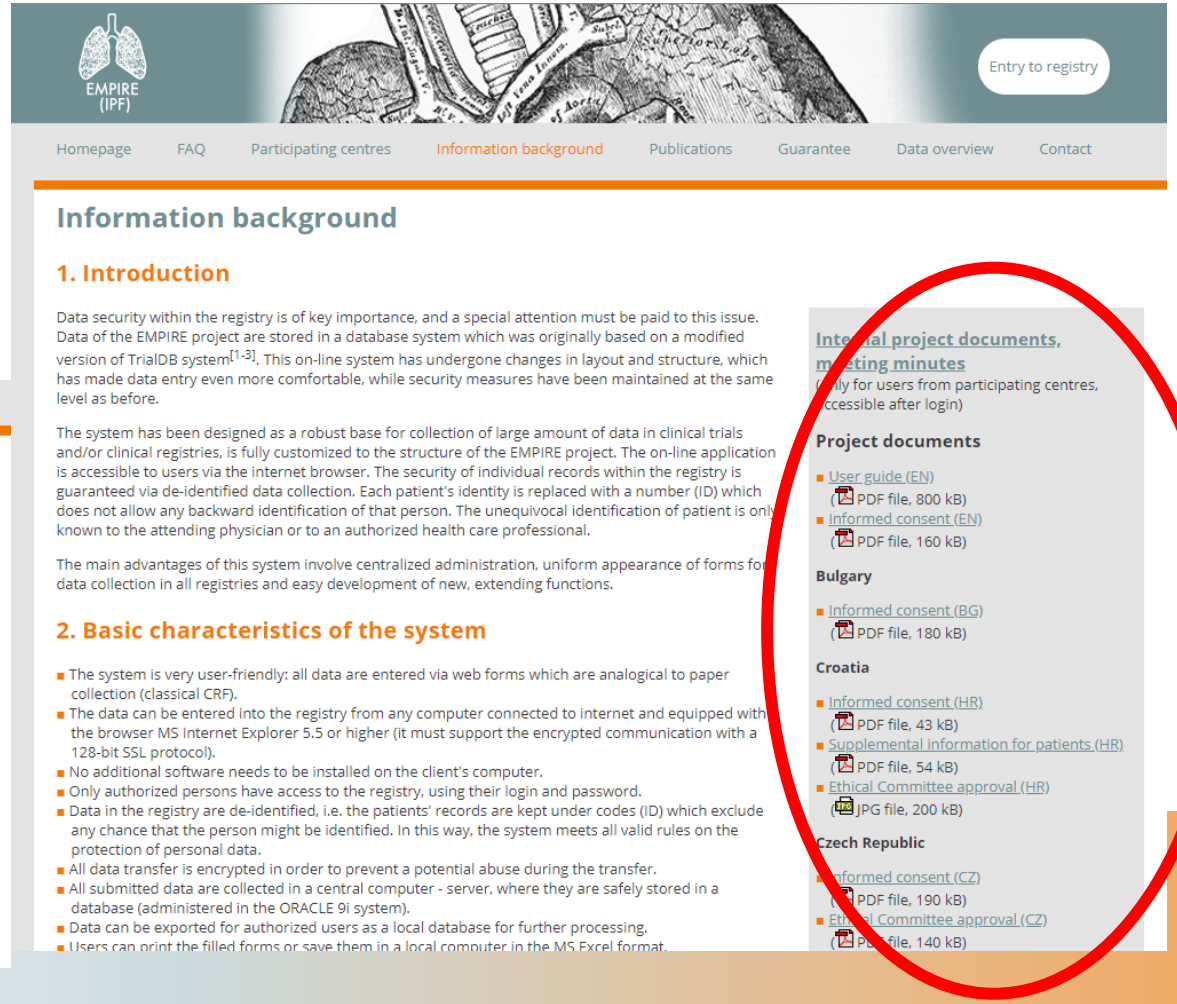
Country	No. of centres with signed contract	No. of centres without signed contract
Czech Republic	8	9
Hungary	1	5
Poland	3	6
Slovakia	3	3
Serbia	2	2
Turkey	0	1
Croatia	1	1
Israel	1	1
Bulgaria	1	0
Austria	2	0
Macedonia	1	0
Total	23	28

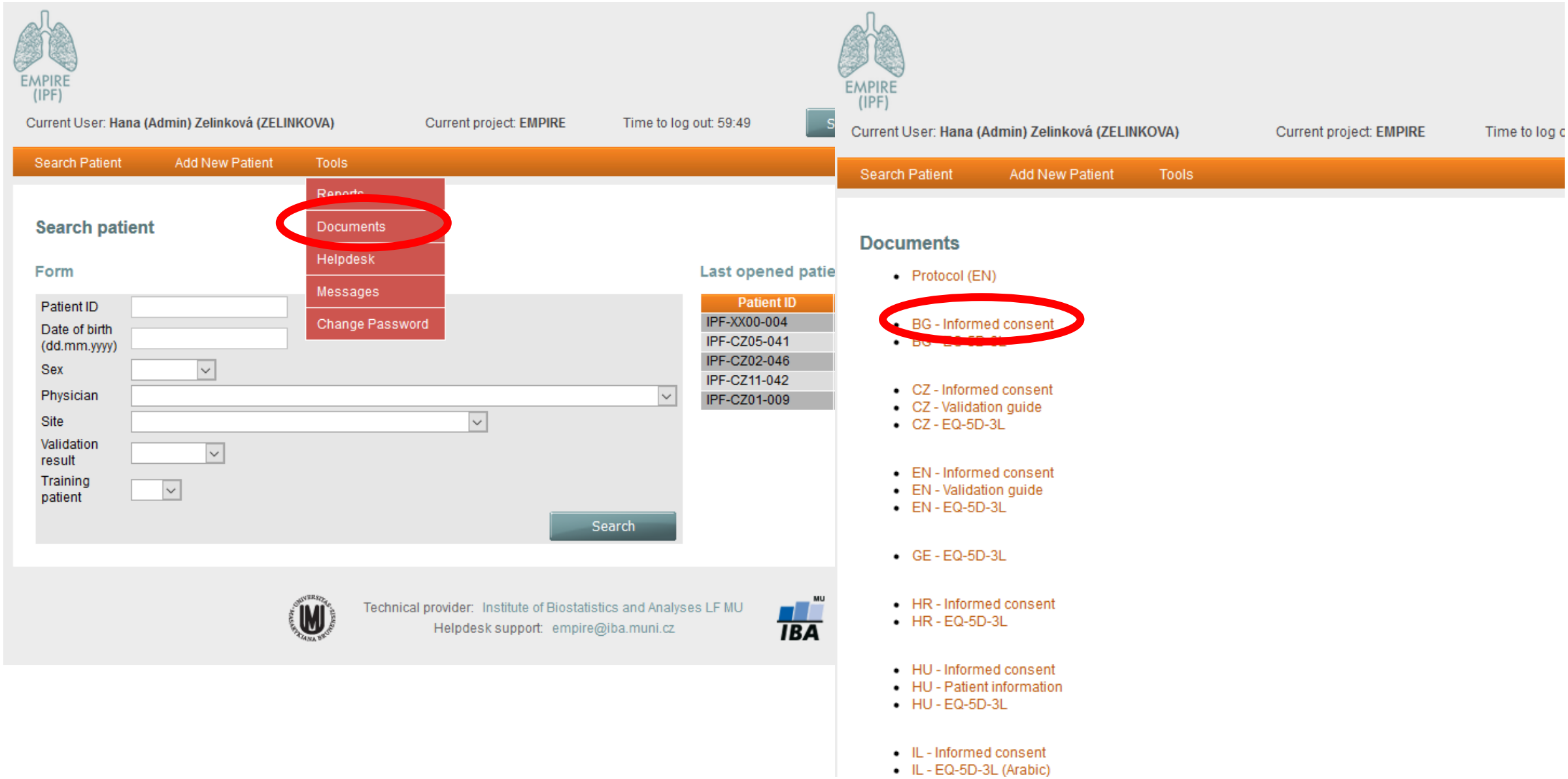
EMPIRE (IPF)

News in the registry

- Informed consents (IC) have been translated into local languages and are available on the project website and in the database itself (together with local versions of IC).
- Meeting minutes and presentations from previous SC meetings have been uploaded on the website.






EMPIRE (IPF)
Current User: Hana (Admin) Zelinková (ZELINKOVA)
Current project: EMPIRE
Time to log out: 59:49
Search Patient
Add New Patient
Tools
Reports
Documents
Helpdesk
Messages
Change Password
Search patient
Form
Patient ID
Date of birth (dd.mm.yyyy)
Sex
Physician
Site
Validation result
Training patient
Search
Last opened patie
Patient ID
IPF-XX00-004
IPF-CZ05-041
IPF-CZ02-046
IPF-CZ11-042
IPF-CZ01-009
Technical provider: Institute of Biostatistics and Analyses LF MU
Helpdesk support: empire@iba.muni.cz
IBA
Documents
Protocol (EN)
BG - Informed consent
CZ - Informed consent
CZ - Validation guide
CZ - EQ-5D-3L
EN - Informed consent
EN - Validation guide
EN - EQ-5D-3L
GE - EQ-5D-3L
HR - Informed consent
HR - EQ-5D-3L
HU - Informed consent
HU - Patient information
HU - EQ-5D-3L
IL - Informed consent
IL - EQ-5D-3L (Arabic)

EMPIRE (IPF)

News in the registry

- Validation excel tables sent – physicians can find here precisely which information is missing, incorrect, unknown, not logical etc. in the data they enter into the database. We would like to ask them to complete all of the missing/incorrect information for their patients.
- The patients with missing IC should sign it; a new version of the IC should be used!

PATIENT_ID	nationality	SITE	NAME	informed_consent	date_diagnosis	date_admission_visit	date_death	reason_death	date_end	height	weight	weight_greater_height	duration_symptoms	duration_greater_200	familiar_ipf	nyha	crepit
IPF-SK05-002	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján					Missing									
IPF-SK05-004	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján													Missing	
IPF-SK05-005	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján													Missing	
IPF-SK05-006	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján													Missing	
IPF-SK05-007	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján													Missing	
IPF-SK05-010	SK	Levice - Ambulancia pneumológie a ftizeológie	Plutinský Ján					Missing									

- De-identification of patients – the FULL DATE OF BIRTH and INITIALS of all patients in the database have been replaced by MONTH and YEAR of birth of the patients. It is possible to input the whole date of birth into the database (day/month/year); however, 10 minutes after that the system will automatically change the day from the date into number 01 (meaning 1st day of the month). Information on month and year (01/month/year) stay as they are in all patients.

Patient ID	Site	Date of birth (dd.mm.yyyy)
IPF-XX01-001	CBA2	01.01.1990
IPF-XX01-002	CBA2	01.01.1965
IPF-XX01-003	CBA2	01.06.1982
IPF-XX01-004	CBA2	01.02.1950
IPF-XX01-005	CBA2	01.06.1975
IPF-XX01-006	CBA2	01.01.1900
IPF-XX01-007	CBA2	01.12.1940
IPF-XX01-008	CBA2	01.01.1970
IPF-XX01-009	CBA2	01.09.1980
IPF-XX01-010	CBA2	01.12.1990
IPF-XX01-011	CBA2	01.06.1963
IPF-XX01-012	CBA2	01.07.1947
IPF-XX01-013	CBA2	01.01.2000
IPF-XX01-014	CBA2	01.01.2000
IPF-XX01-015	CBA2	01.07.1960
IPF-XX01-016	CBA2	01.01.1950

EMPIRE (IPF)

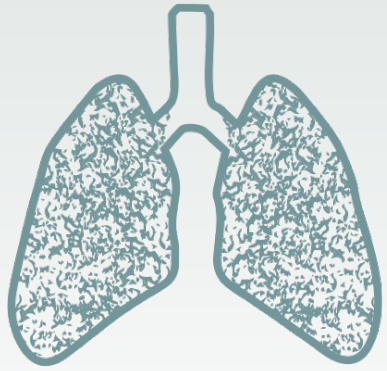
Financial support

- After a meeting in January 2019, **Boehringer Ingelheim RCV and Roche Global agreed on supporting the EMPIRE Registry in the years 2019–2021**; contract preparation is currently underway.

- Since December 2017, an active contract with **Roche CZ** has been effective, which has supported an IIS study (financial support of the Czech part of the registry) led by Prof. Vašáková till the end of 2020. **This contract will be probably terminated by the new contract with Roche Global.**

- In cooperation with the Roche Global an IIS study *Assessing pirfenidone effectiveness in possible UIP and possible/probable IPF patients and characterizing natural history of IPF progression* is being prepared in order to support the registry. The contract/protocol/SAP is currently being finalized.

EMPIRE
(IPF)



Overview of SC members' votes since previous meeting

MUNI MED Institute of Biostatistics and Analyses

Mortality and progression free survival in the IPF patients. Real world data from EMPIRE registry

- An abstract for ERS 2019 by Prof. Vašáková

- Data from the whole EMPIRE registry
- Hypothesis is that the patients on antifibrotic treatment have longer total and progression-free (i.e. decline of 10% VC or 15% TLCo compared to the initial value – at the treatment initiation) survival than those on any other treatment modalities. This effect also depends on the initial VC and TLCO values (i.e. at the time of treatment initiation).

- Proposal approved by all SC members
- Prof. Kjaeva and prof. Studnicka did not react

EMPIRE
(IPF)

Removal of stopping rules in the Czech Republic

- IBA MU can prepare analyses from the whole EMPIRE data as a basis for the cost-effectiveness analyses, according to which the stopping rules for IPF treatment may be removed by the regulatory authority in the Czech Republic. The analyses will be provided to the Roche company.

- The analyses may be used for publication

- Approved by all SC members

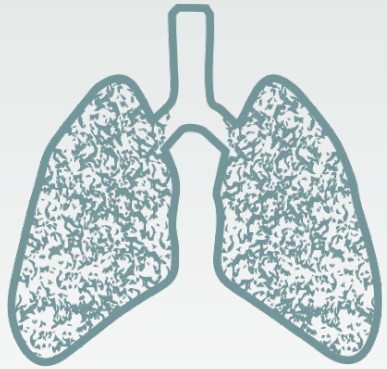
EMPIRE
(IPF)

Participation of BI, Roche, Prof. Suissa and Dr Walsh in SC meeting

- A vote on the participation of EMPIRE supporters (BI, Roche and external professionals with whom we cooperate – Prof. Suissa and Dr Walsh) in the SC meeting in Geneva

- Approved by all SC members
- Prof. Kjaeva did not react

EMPIRE (IPF)



Outcomes & publications

Published and accepted articles

- **Effect of pirfenidone on lung function progression and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry**
  Lead author: Dr. Monika Žurková
  Published in *Respiratory Research*

- **Long-term effects and adverse events of nintedanib therapy in IPF Patients with functionally advanced disease**
  Lead author: Dr. Eniko Barczi (Hungary)
  Accepted for publication in *Advances in Therapy*

EMPIRE (IPF)

Submitted articles

- **Prognostic factors in idiopathic pulmonary fibrosis: The European MultiPartner IPF Registry (EMPIRE) from Central and Eastern Europe**
  Lead author: Tanja Tran
  Submitted for publication in the American Journal of Respiratory and Critical Care Medicine with the deadline on 1 March 2019

EMPIRE (IPF)

Manuscripts in preparation

- **Comorbidity in IPF patients from EMPIRE registry (European Multipartner IPF registry)**
  Lead author: Dragana Jovanovic
  Currently at BI – waiting for an external medical writing organization to give an opinion

- **Bleeding risk in Central European IPF patients treated with different anticoagulants**
  Lead author: Prof. Veronika Müller
  Currently sent to BI, looking for a journal for publication

- **On genetic polymorphisms in Czech patients**
  Dr. Doubková, Dr. Žurková, doc. Kriegrová

EMPIRE
(IPF)

Submitted abstracts for ERS

- **Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry**
  Lead author: Prof. Vašáková

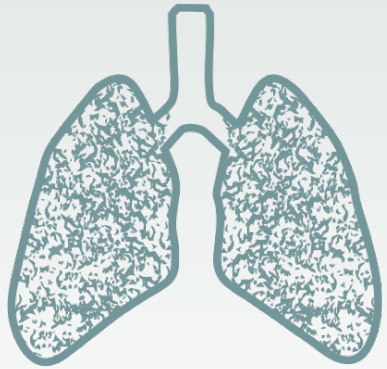
- **Differences between ANCA positive and negative lung fibrosis cases without vasculitis**
  Lead author: Prof. Mogulkoc (Turkish patients only)

EMPIRE
(IPF)

Analyses underway

- An analysis to support removal of stopping rules in the Czech Republic
- A preliminary report (a simpler version of the summary report) which will be posted on website
- 3 analyses aimed at genetic polymorphism in Czech patients from EMPIRE IPF Registry
  - Analyses are focused on drug metabolism, MUC5B polymorphism, TERT/ TERC genes mutations,
  - Analysis for Dr. Doubková is being finished, we are waiting for parameters to be specified for the remaining 2 analyses for Dr. Lošťáková, doc. Kriegrová
- Country reports
- Assessing pirfenidone effectiveness in possible UIP and possible/probable IPF patients and characterizing natural history of IPF progression
  - IIS led by Prof. Vašáková, supported by Roche Global

EMPIRE (IPF)

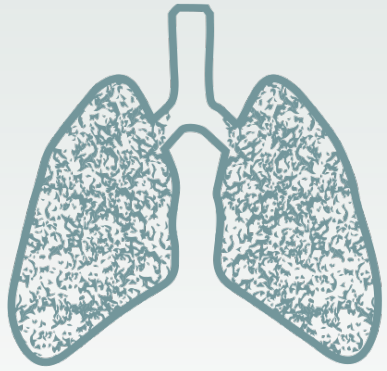


IIS proposals

IIS proposals

- Any SC member can ‘apply’ for writing a manuscript according to any IIS/analysis done – a rule **‘first come, first served’**
- **Planed IIS studies**
  Any new suggestions?

EMPIRE (IPF)



EMPIRE subprojects

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HRCT

HRCT repository and data warehouse for (re)assessment of HRCT images

- Arranged in cooperation with a team of expert radiologists led by Dr Simon Walsh.
- Main focus will be put on the development of imaging biomarkers of early progression on the probably biggest HRCT imaging cohort in the world.
- The collected scans will be evaluated according to the new radiological criteria for the IPF diagnostics. It will correlate with patient's prognosis (mortality, decrease of VC and TLco in time and with respect to the treatment).
- HRCT images will be inter-connected with primary EMPIRE registry records (patient level links).

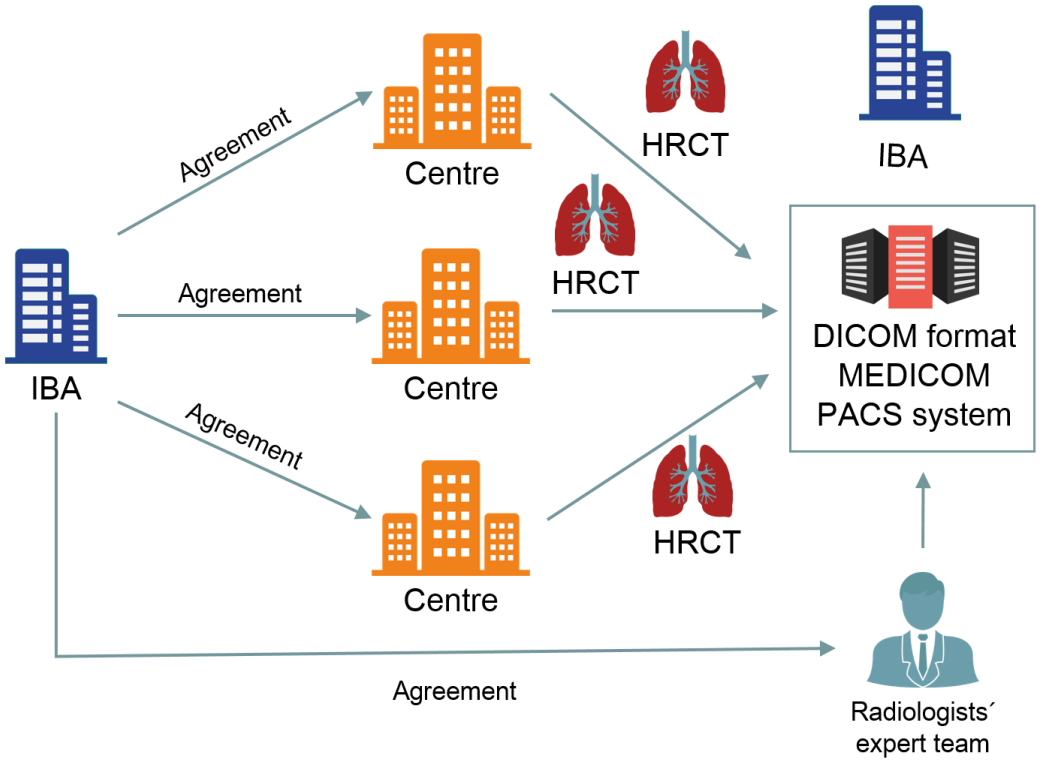
- There will be a retrospective and prospective data collection.
- The protocol and the budget of the subproject are completed.
- A new informed consent should be prepared.

EMPIRE
(IPF)

HRCT

Prospective HRCT images evaluation

- The assessment of HRCT images of living patients and associated data processing will be performed via their collection in a centralized repository – MEDICOM – professional DICOM information PACS system (which works at expert level at Masaryk University, Brno, Czech Republic).
- The continuous centralization of images will be only based on a **signed informed consent of living patients**.
- As the current informed consent does not involve information about the HRCT images collection, a specific informed consent will have to be prepared and signed by patients for this purpose.

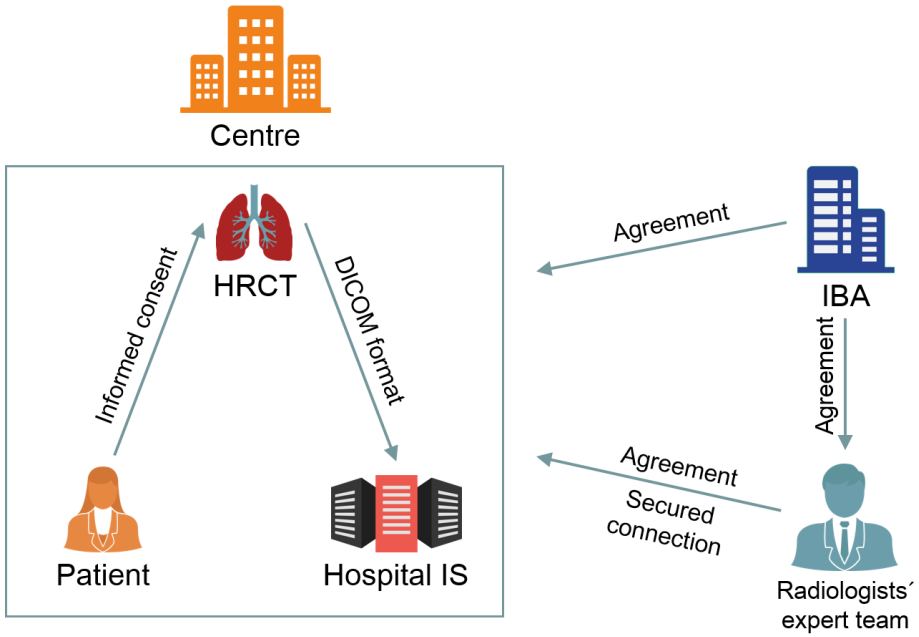


EMPIRE
(IPF)

HRCT

Retrospective HRCT images evaluation

- The assessment of HRCT images of dead patients and associated data processing will be performed via direct collaboration of centres and the team of expert radiologists (and its deputies/Steering Committee members in each EMPIRE country). The expert radiologists team assessing HRCT images will contact the clinical centres directly and (based on mutual agreement) get the access to the patient's HRCT images stored as a part of their electronic medical records in a particular centre. The records should be in DICOM format (DICOM protocol). Afterwards the team of expert radiologists will assess the images. Both assessment and recording of its outcomes are managed according to rules adopted by a particular clinical centre.
- GDPR regulation is not related to dead people; therefore, it is also possible to send the HRCT images of dead patients directly to the central repository. Needs to be further discussed.



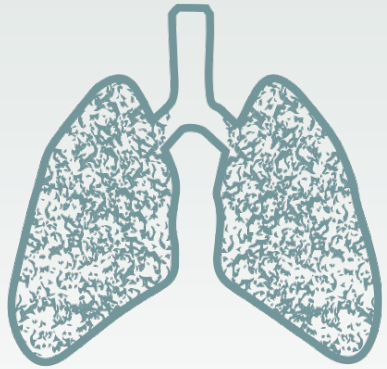
EMPIRE (IPF)

PD-L1 biomarkers

- Team of Prof. Jovanovic performed a soluble sPD-L1 test to determine concentrations in blood plasma in 23 IPF patients.
- Prof. Jovanovic has now a sufficient leftover of the platform for this sPD-L1 blood test, (500 tests (kits) for PD-L1 + 80 for SAA 1) and would be able to provide it to the EMPIRE team to have a joint project on this issue, which would be performed for free by her colleague, a biochemist Prof. Jelena Kotur.

- We are currently trying to find out ways of how to deal with the complicated logistics and transfer of biomaterial from (max) 10 different countries to Serbia – we need more details on how many samples will be sent from each hospital, what is their approximate weight etc. in order to calculate the budget.
- Protocol is currently being prepared in cooperation with prof. Jovanovic
- New informed consent for the subproject will be needed.

EMPIRE
(IPF)



EMPIRE
(IPF)

Changes in eCRF

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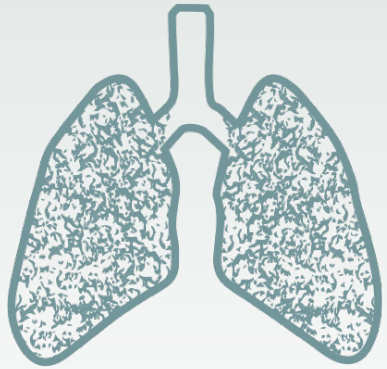
Proposal of prof. Mogulkoc

Could the options for the categorization of the HRCT appearances be updated to bring them into line with the four diagnostic categories currently recommended by ATS/ERS (usual interstitial pneumonia (UIP) pattern, probable UIP pattern, indeterminate pattern and alternative diagnosis)?

- Currently we have options in the database for HRCT pattern – UIP pattern, UIP pattern possible, Pattern inconsistent with UIP
- In the section Histopathological finding we have options – Probable UIP, Possible UIP, Unclassifiable fibrosis, Inconsistent with UIP, Not done

If we go for the change in HRCT pattern according to the new categorization, how would we deal with the patients that had the HRCT pattern in the database according to the ‘old’ categorization?

EMPIRE
(IPF)



EMPIRE
(IPF)

Registry rules, contracts, payments

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Publications submission

- Prior to any written, oral or audio-visual publications (manuscript, poster, abstract, presentation) of the results they have to be sent to Boehringer Ingelheim **at least sixty (60) days in advance** (unless otherwise agreed with BI in individual cases) – you can send it to IBA and we will resend it to BI.

- To check whether all information presented/published are in line with SmPC and are compliant with their internal regulations. To protect a patentable invention or to avoid disclosure of Confidential Information, trade secrets or know-how. It is a fairly formal review of the manuscript/abstract.

- BI would like to support the publications and **help to raise their scientific value** by providing a medical writer who could add scientifically relevant supplementary information, be the advisory body for the author of the publication; they have no aim in changing the content.

- Do not forget to add a statement regarding the BI support.

Access to patients' records within centres/countries

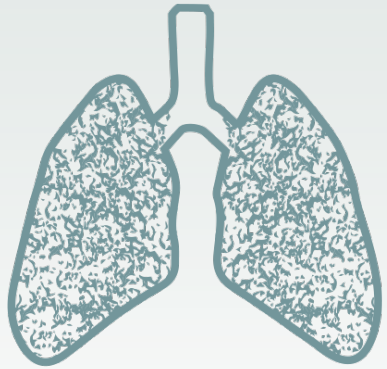
- **Current state:** data managers/physicians from involved centres can only see records of patients from their particular centre. A guarantor from each country (SC member) can see all patients from his/her country.
- Is there a consensus to continue in this practice? Is it neccessary and ethical if we do not have written consent (permission) from all centres provided?

EMPIRE
(IPF)

Promotion of the registry on a larger scale

- How would the SC members like to present EMPIRE?
- Suggestion to organize a press conference about the EMPIRE project at some international congress (not necessarily ERS)
- IBA will prepare an annual report about the Registry, which will be published on the website (above-mentioned presentation – 'simplified summary report')
- Regular update of the website
- By the end of Q2 IBA should prepare a preliminary report about the EMPIRE Registry – it will inform about the past year (2018) and following plans (including subprojects)

EMPIRE
(IPF)



Data management and statistical analysis

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Data quality considerations

- Loss of observations in time is a key issue
  - decreasing statistical power
  - possible introduction of bias
- Correction of data
  - In early February validation Excel tables were sent separately to each centre.
  - The tables included information about missing or incorrect patient data in the database.
  - In order to improve the outcomes of the EMPIRE database, it is necessary to complete the invalid records with missing and/or correct data.
- Design considerations
  - statistical analysis should be planned a and performed bearing in mind the limitations of real-world longitudinal data

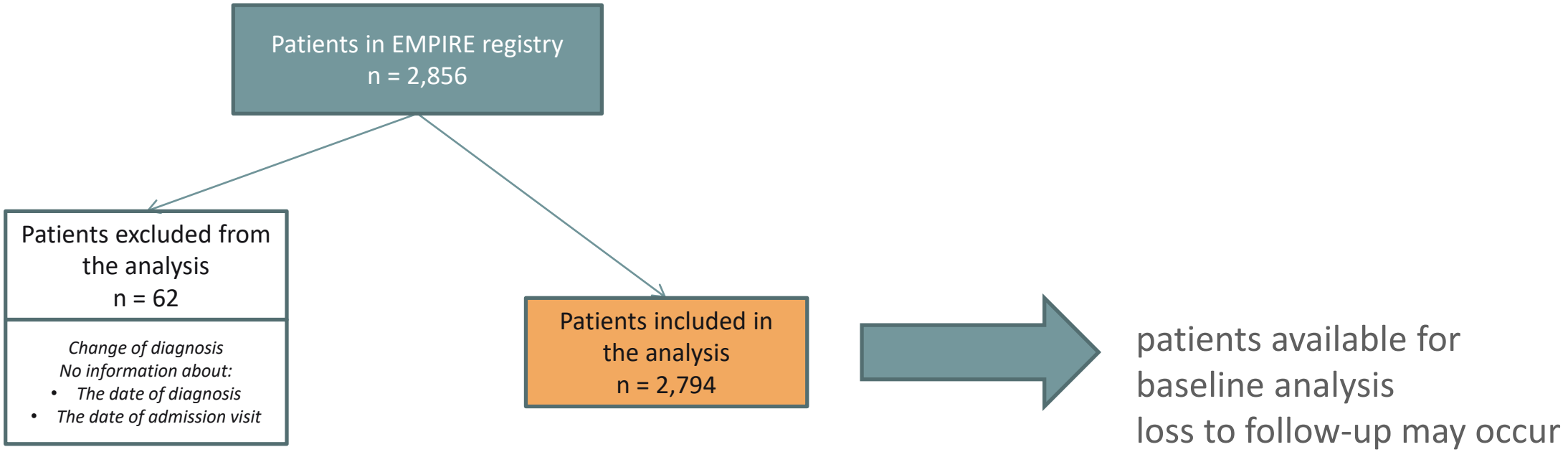
EMPIRE (IPF)

Statistical analysis considerations

- Incomplete follow-up data – the most important limitation for data analysis.
- Ways of working with follow-up data in longitudinal analysis:
  - **Analytical classification** of follow-up visits into time categories (6-month visit, 1-year visit, etc.) – problem of variability of dates of visit; completeness of follow up data is crucial
  - **Strictly defined dates of follow-up visits** (a physician selects time category of the visit **in the registry**) – clinical decision instead of analytical stratification
  - **Time to event analysis** – survival analysis; for progression defined by a change of variable between time points, the problem with follow-up data completeness and variability of dates of visits still persists
- **Three scenarios of selection of start of follow for the analysis:**
  - Starting point is the date of diagnosis
  - Starting point is the date of first visit (enrolment)
  - Starting point is the start of treatment (pirfenidone/nintedanib)
  - **Appropriate analysis setting should be considered when planning the analysis**

EMPIRE (IPF)

Analysis flow-chart (22/1/2019)



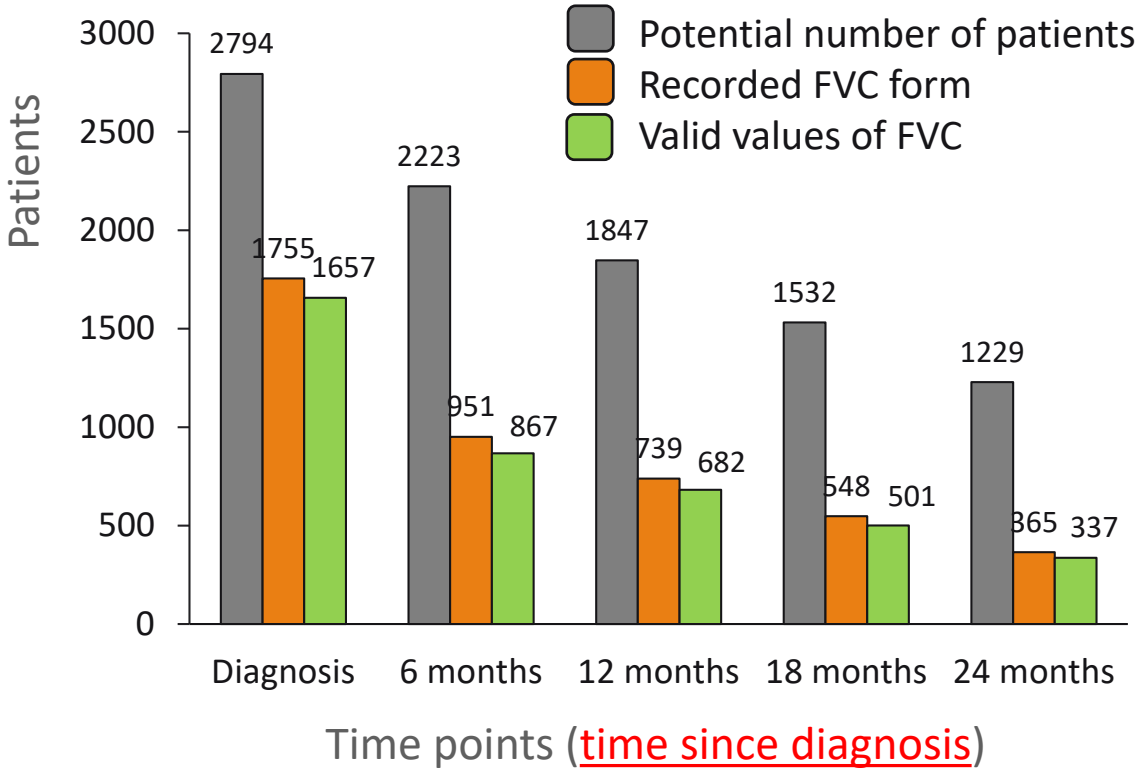
EMPIRE (IPF)

Comparison of patients suitable for analysis and theoretical number of patients

Potential number of patients is number of patients recorded in registry minus deceased patients and patients with insufficient follow-up length at given time point.

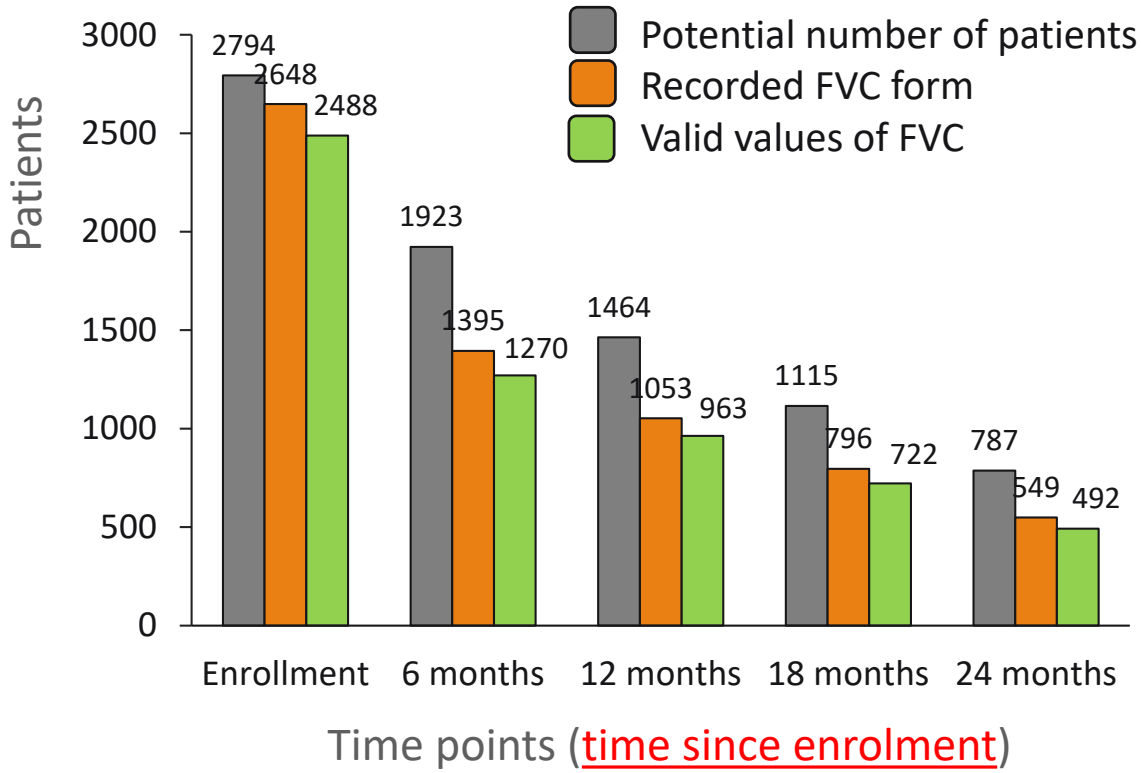
Analysis scenario: Since diagnosis

N potential	2794	2223	1847	1532	1229
Deceased	-	72	156	242	316
Short FU	-	499	791	1020	1249



Analysis scenario: Since enrolment

N potential	2794	1923	1464	1115	787
Deceased	-	157	264	369	448
Short FU	-	714	1066	1310	1559



EMPIRE (IPF)

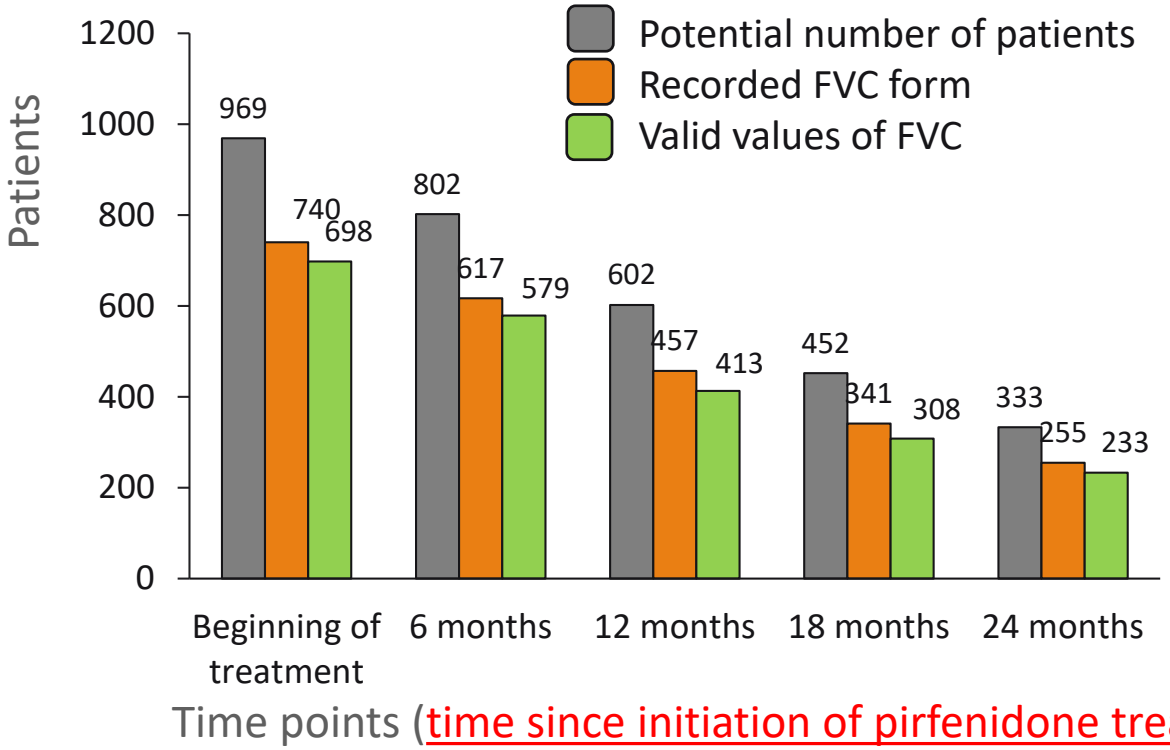
Follow-up visit recorded within 2 months of the reference date

Comparison of patients suitable for analysis and theoretical number of patients

Number of patients with treatment by pirfenidone (**there are 969 treated by pirfenidone**).
Potential number of patients is number of patients recorded in registry minus deceased patients and patients with insufficient follow-up length at given time point.

Analysis scenario: Since initiation of pirfenidone treatment

N potential	969	802	602	452	333
Deceased	-	43	94	140	175
Short FU	-	124	273	377	461



EMPIRE (IPF)

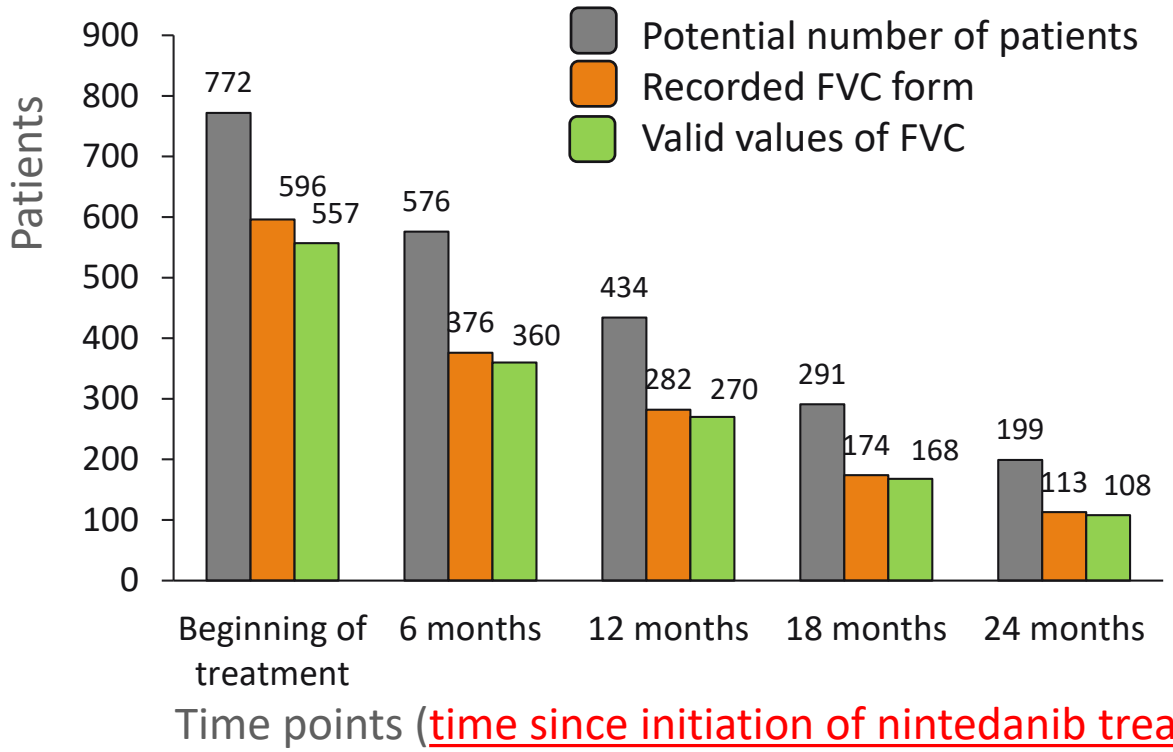
Follow-up visit recorded within 2 months of the reference date

Comparison of patients suitable for analysis and theoretical number of patients

Number of patients with treatment by nintedanib (**there are 772 treated by nintedanib**).
Potential number of patients is number of patients recorded in registry minus deceased patients and patients with insufficient follow-up length at given time point.

Analysis scenario: Since initiation of nintedanib treatment

N potential	772	576	434	291	199
Deceased	-	173	288	409	492
Short FU	-	23	50	72	81



Follow-up visit recorded within 2 months of the reference date

EMPIRE (IPF)

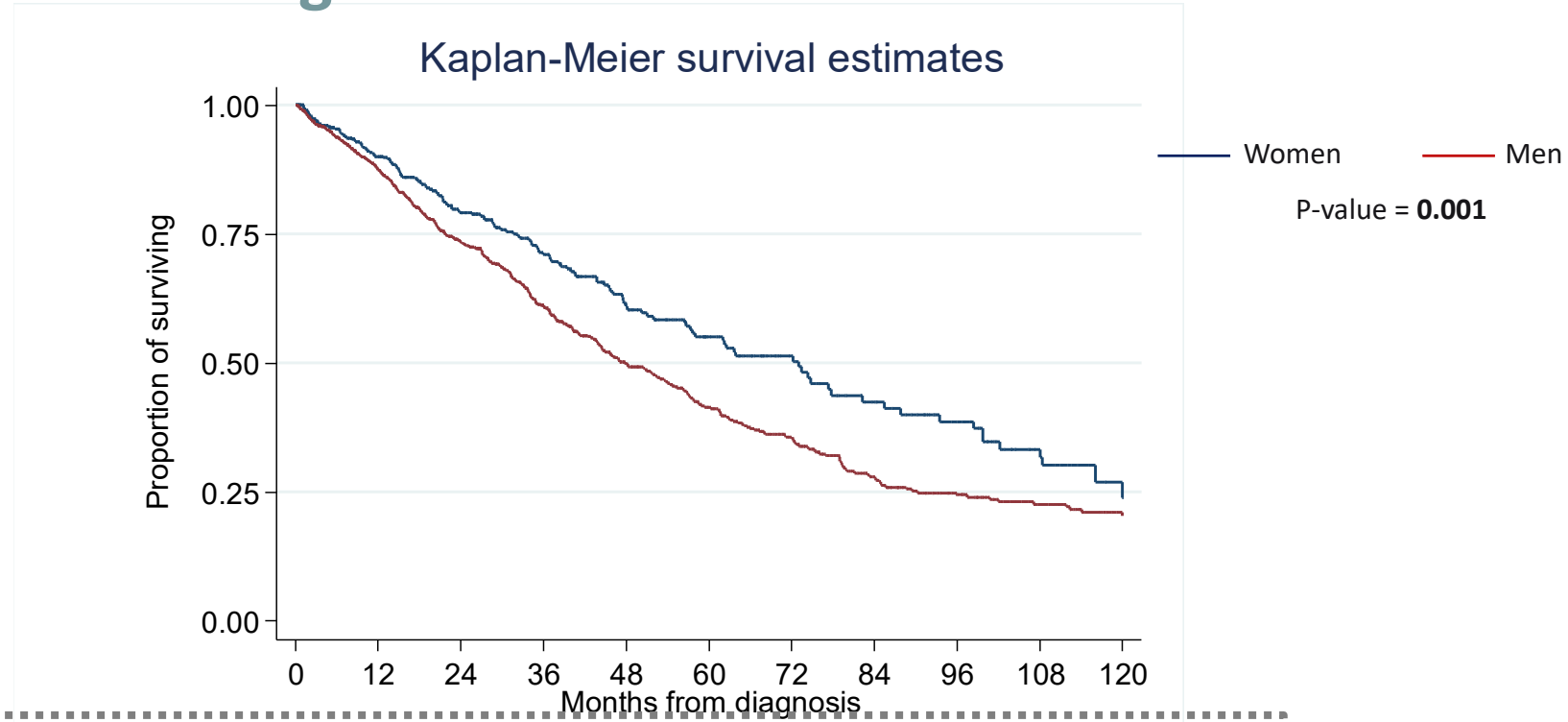
Survival analysis from the time of diagnosis: statistical considerations

- **Long-term survival from the time of diagnosis**
- **Statistical issue of "left truncation"**
  - person is **at risk of death** after diagnosis but before the enrolment (when **not under observation**)
  - had the person died before arriving at our door, we would never have known about her
  - necessary to treat her subsequent survival time as conditional on having already survived the time before enrolment
- **Left truncation possible to adjust for within the statistical analysis**
- **Previously including both naive (marked as "without admission visit") and left truncation adjusted (marked as "with admission visit") Kaplan-Meier curve**
- **Now only correct estimation was kept in the summary report**
- **Cautiously interpret n at risk**

Stata survival analysis reference manual, release 14

EMPIRE (IPF)

Long-term survival according to sex

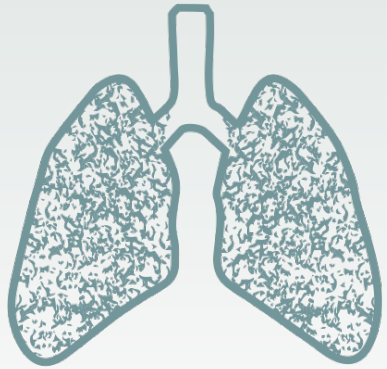


Sex	Median of survival (months)	1-year survival (95% CI)	5-year survival (95% CI)	10-year survival (95% CI)
Women	109.8	0.938 (0.917–0.954)	0.697 (0.645–0.743)	0.446 (0.348–0.540)
Men	79.0	0.924 (0.909–0.936)	0.592 (0.556–0.626)	0.383 (0.331–0.434)

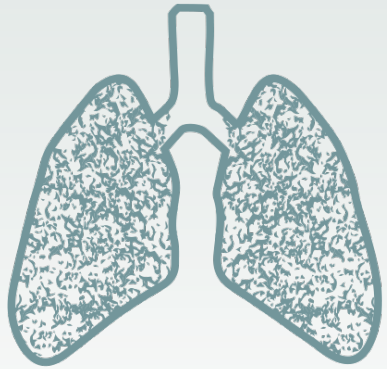
EMPIRE (IPF)

Any other issues, proposals?

EMPIRE
(IPF)



Time for discussion



Thank you for your time and attendance to the 9th international SC meeting!

MUNI MED Institute of Biostatistics and Analyses