



EMPIRE
(IPF)

European **M**ulti**P**artner **I**PF **R**Egistry

8th international SC meeting

Martina Vašáková¹, Filip Kňážek²

1-Thomayer Hospital, Prague, Czech Republic;

2 – Faculty of Medicine, Masaryk University





Current status of the registry

Representation of countries in EMPIRE registry

- Czech Republic (10 sites)
- Hungary (6 sites)
- Poland (9 sites)
- Slovakia (6 sites)
- Serbia (3 sites)
- Turkey (1 site)
- Croatia – (3 sites)
- Israel – (1 site)
- Bulgaria – (1 site)
- Austria – (1 site Salzburg)
- Macedonia – (1 site Skopje)



New centres interested in EMPIRE

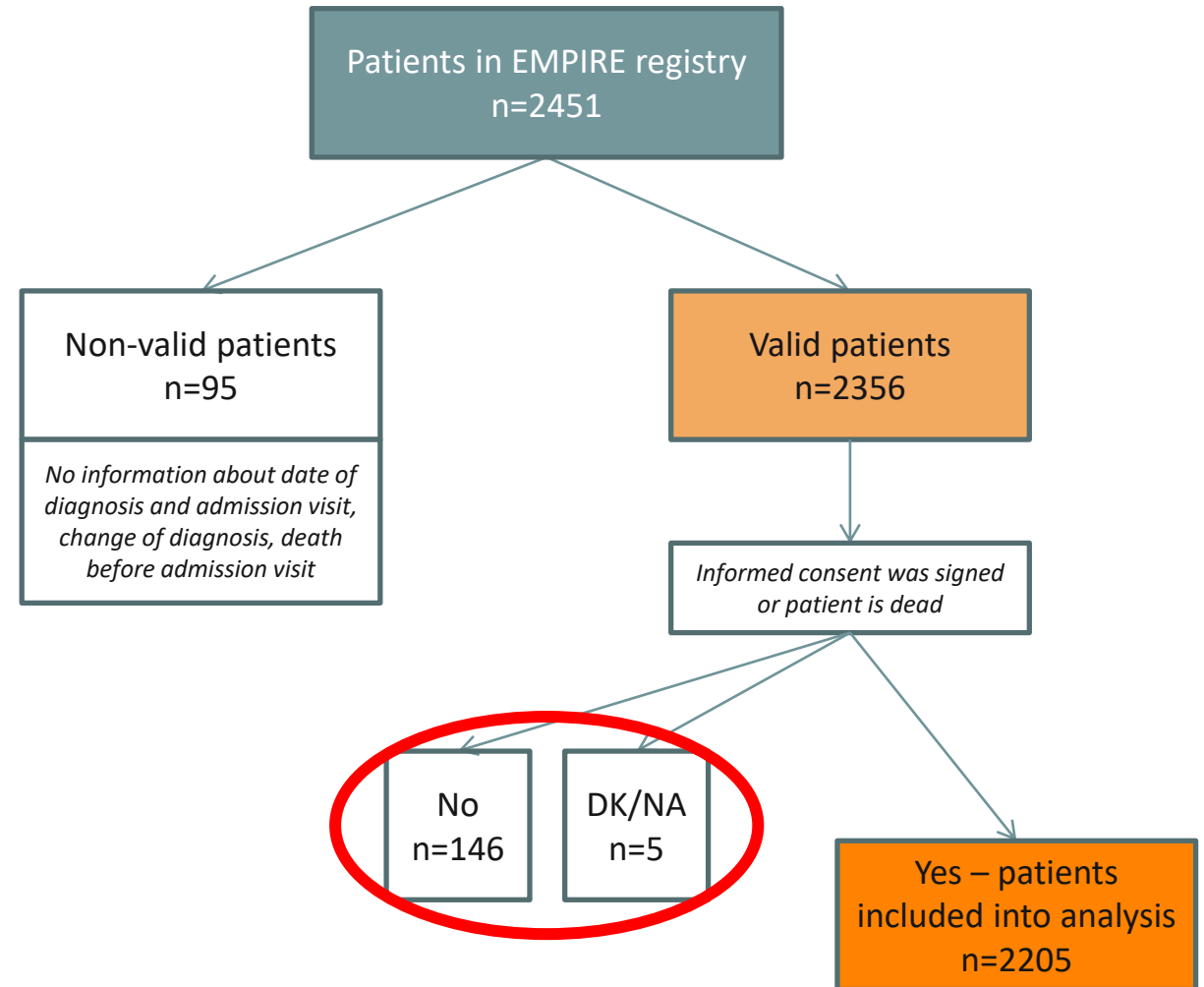
| Country | Comment |
|---------|----------------------------------------------------------------------------------------------------------|
| Poland | 1 new site will be joining the registry (we have EC approval, contract sent) |
| Hungary | 3 new sites want to join the registry (we have EC approval, contract sent) |
| Serbia | 1 new site wants to join the registry (missing EC approval, contract, negotiation ongoing) |
| Austria | 1 new site would like to join registry (we have EC approval, contract sent) |
| Romania | Negotiation with Irina Strambu about possibility to join the registry with 5 sites (negotiation ongoing) |
| Latvia | Latvia would like to join EMPIRE (core information + documents sent to Alvils Krams) |
| Israel | 1 new centre (waiting for EC approval, negotiation ongoing) |
| Turkey | centres from Turkish Respiratory Society (contact from prof Jovanovic, negotiation ongoing) |



Number of patients by countries in EMPIRE registry

n=2205

| | N (%) |
|----------------|-------------|
| Czech Republic | 751 (34.1%) |
| Poland | 434 (19.7%) |
| Turkey | 429 (19.5%) |
| Hungary | 206 (9.3%) |
| Slovakia | 166 (7.5%) |
| Israel | 82 (3.7%) |
| Serbia | 67 (3.0%) |
| Croatia | 62 (2.8%) |
| Bulgaria | 8 (0.4%) |



date of export: 18.6.2018



News in registry

- **EMPIRE Registry protocol - updated to version 2.0**
 - Mainly points 8 (Regulatory and Legislative Requirements), 9 (Training of Investigators Confidentiality) and 10 (Pharmacovigilance) have been updated
 - Roles and processes in the project and communication updated as well
 - Approved by Czech Ethics Cmommittee (EC), has to be approved by EC in each country and than send to IBA – SC members should help with **the multicentre approval od EC**, if local approval is needed the centre should send it itself

News in registry

- **New version of informed consent (IC)**
 - Updated according to the GDPR regulation
 - Needs to be **translated into local languages** and sent to IBA (me) with a **proof (certificate) of translation** – SC members may be of a great help with this
 - For the patients in which IC is **missing it should be provided**, each of the living patients **should sign a new version** of IC

All of the documents will be updated on the web and in the database itself (together with local versions of IC).

The publication list is currently being updated and will be updated regularly every month.



Background information

1. Introduction

Data security within the registry is of key importance, and a special attention must be paid to this issue. Data of the EMPIRE project are stored in a database system which was originally based on a modified version of TrialDB system^[1-3]. This on-line system has undergone changes in layout and structure, which has made data entry even more comfortable, while security measures have been maintained at the same level as before.

The system has been designed as a robust base for collection of large amount of data in clinical trials and/or clinical registries, is fully customized to the structure of the EMPIRE project. The on-line application is accessible to users via the internet browser. The security of individual records within the registry is guaranteed via de-identified data collection. Each patient's identity is replaced with a number (ID) which does not allow any backward identification of that person. The unequivocal identification of patient is only

Roles and processes in the project, meeting minutes

(only for users from participating centres, accessible after login)

Project documents

- [User guide \(EN\)](#)
(PDF file, 800 kB)
- [Informed consent \(EN\)](#)

Authentication for users from participating centres – login is the same as the login to the registry

| | |
|------------------|-------------------------------------|
| Username: | <input type="text"/> |
| Password: | <input type="password"/> |
| | <input type="button" value="Send"/> |



→ **Are you user of the registry and have you forgotten your password?**

Please contact our help desk staff.



Přihlášený uživatel: Filip Kňážek (KNAZEK)

Projekt: EMPIRE

Čas do odhlášení: 59:53

Vyhledávání

Nový pacient

Nástroje

Dokumenty

Helpdesk

Zprávy

Změna hesla

Vyhledání pacienta

Formulář

| | |
|---------------------------------------|----------------------|
| ID pacienta | <input type="text"/> |
| Datum narození | <input type="text"/> |
| Pohlaví | <input type="text"/> |
| Iniciály | <input type="text"/> |
| Lékař | <input type="text"/> |
| Centrum | <input type="text"/> |
| VILP | <input type="text"/> |
| Výsledek validace | <input type="text"/> |
| Cvičný pacient | <input type="text"/> |
| <input type="button" value="Hledej"/> | |

Naposledy otevření p

| ID pacienta | Pac |
|--------------|-------|
| IPF-CZ13-212 | 24.08 |
| IPF-CZ16-015 | 24.08 |
| IPF-CZ05-029 | 03.08 |
| IPF-BG01-001 | 03.08 |
| IPF-CZ01-008 | 03.07 |



Technické zajištění: Institut biostatistiky a analýz LF MU

Podpora projektu: empire@iba.muni.cz



Přihlášený uživatel: Filip Kňážek (KNAZEK)

Projekt: EMPIRE

Čas do odhlášení: 59:56

Vyhledávání

Nový pacient

Nástroje

Dokumenty

- Protocol (EN)
- BG - Informed consent
- BG - EQ-5D-3L
- 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)
- IL - EQ-5D-3L (Hebrew)
- IL - EQ-5D-3L (Russian)
- PL - Informed consent
- PL - Patient information
- PL - EQ-5D-3L
- PL - EQ-5D-3L feminine
- PL - EQ-5D-3L masculine
- RS - EQ-5D-3L
- RS - EQ-5D-3L cyrillic
- SK - EQ-5D-3L



Publications and presentations

[2017](#) | [2016](#)

2017

Articles in international journals

- Doubková M, Švancara J, Svoboda M, Šterclová M, Bartoš V, Plačková M, Lacina L, Žurková M, Binková I, Bittenglová R, Lošťáková V, Merta Z, Šišková L, Tyl R, Lisá P, Šuldová H, Petřík F, Pšikalová J, Řihák V, Snížek T, Reiterer P, Homolka J, Musilová P, Lněnička J, Palúch P, Hrdina R, Králová R, Hortvíková H, Strenková J, Vašáková M. [EMPIRE Registry, Czech Part: Impact of demographics, pulmonary function and HRCT on survival and clinical course in idiopathic pulmonary fibrosis](#). *The Clinical Respiratory Journal* 2017 [Epub ahead of print].

Presentations at international conferences

News in registry

- New **subproject** under the EMPIRE Registry should be made, regarding **the collection of HRCT images** from the whole registry in cooperation with Dr. Simon Walsh
- The HRCT images should be stored in Czech Republic in PACS system – we will start with the negotiation



Financial support

- Active contract with **Boehringer Ingelheim RCV** till the end of year 2019
- Since December 2017 active contract with **Roche CZ** supporting IIS study (financial support of the Czech part of the registry) led by prof Vašáková till the end of year 2020
- Together with **Roche Global** 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





EMPIRE
(IPF)

Vote overview of SC members since previous meeting

Rules for voting

- **Email** – answer **Agree/ Disagree**
- Other options (**Doodle**, **Survey Monkey**)

8th Steering Committee Meeting
15.09.2018
by Filip Křáček • 28 minutes ago • Print

📍 Paris
Paris, France

🕒 All times displayed in Europe/Prague

Table Calendar

| | Sep 15 SAT | Sep 15 SAT | Sep 15 SAT | Sep 15 SAT |
|----------------|--------------------|--------------------|--------------------|--------------------|
| | 4:00 PM 6:30 PM | 5:00 PM 7:30 PM | 6:00 PM 8:30 PM | 7:00 PM 9:30 PM |
| 1 participant | ✓1 | ✓1 | ✓1 | ✓1 |
| ⊕ Filip Křáček | ✓ | ✓ | ☐ | ☐ |
| ⊕ Filip Křáček | ✓ | ✓ | ✓ | ✓ |

✓2 Send

Survey


1. Do you like surveys? 🛠

☐ Yes

☐ No

☐ Maybe

Done

Powered by
 **SurveyMonkey**
See how easy it is to [create a survey](#).

Rules for voting

3 emails will be sent

- 1st informational
- 2nd and 3 rd reminders
- if there is no answer on the 3 rd email within 3 days, it is counted as agreed



Effect of antifibrotic treatment of IPF in real world

- **Raw dataset for analysis which should be made by professor Suissa**
 - Data from the whole EMPIRE registry
 - Collection of different biomarkers, (i.e. HRCT, BAL Lymphocytosis, VC and TLco at treatment initiation, gender, age) which can predict which drug to use
 - Cooperation with prof. Suissa already approved by SC in 7th SC meeting, **however there has to be an confidentiality/cooperation agreement signed between the University and any third party (professor) that would like to get the raw dataset**
- ✓ **Proposal approved by all SC members**
confidentiality/cooperation agreement has to be signed first



Effectiveness of Proton Pump Inhibitors in IPF

- **Analysis supporting the thesis that proton pump inhibitors are not associated with a reduced mortality in IPF.**
 - At the end there will be raw data set provided (the same as in previous case) to professor Suissa and his student Tanja Tran
- ✓ **Approved by all SC members**
confidentiality/cooperation agreement has to be signed first with professor Suissa



Comorbidity in IPF patients from the EMPIRE

- **Additional analysis for the publication of professor Jovanovic**
 - Median overall survival according to the number of comorbidities, Mortality according to major comorbidities, survival regarding treatment and number of comorbidities will be collected
- ✓ **Approved by all SC members** (apart from prof Kramer who did not answer)
- ✓ **Analysis done**



Velcro crackles in IPF

- **Analysis for Univ.-Prof. Dr. Studnicka/ Dr. Zembacher**
 - Evaluation of velcro crackles as diagnostic and possible prognostic marker for IPF.
 - ✓ **Approved by all SC members**
 - ✓ **To be discussed if needed**





EMPIRE
(IPF)

Publications in progress

Submitted abstracts for ERS congress 2018

| Title | 1 st author | Submission |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------|
| Does body mass index have prognostic significance for patients with idiopathic pulmonary fibrosis? | Nesrin Mogulkoc | ERS |
| Differences in baseline characteristics of newly diagnosed IPF patients in the EMPIRE countries | Veronika Müller | ERS |
| Bleeding risk in IPF patients treated with different anticoagulants: Real world data from the European MultiPartner IPF REgistry (EMPIRE) | Veronika Müller | ERS |
| Real world idiopathic pulmonary fibrosis in the EMPIRE registry | Martina Vašáková | ERS |



EMPIRE manuscripts

- **Professor Samy Suissa together with his student Tanja Tran submitted manuscript of an article „Idiopathic pulmonary fibrosis in Central and Eastern Europe: the European MultiPartner IPF Registry (EMPIRE)“**
- **It was unfortunately **declined** for publication in the ERJ**

Additional analysis on predicitive markers will have to be done

- history of smoking
- co-morbidities: GERD, pulmonary hypertension, arterial hypertension, COPD, obstructive sleep apnea, heart disease, diabetes mellitus, respiratory infections, lung cancer, depression, emphysema
- - NYHA grade
- - UIP pattern
- - QoL
- **Voting - For: Against:**



Articles in progress

- **Article: Effect of pirfenidone on lung function progression and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry**
 - 1 st author Dr. Žurková, currently final revisions, Respiratory Medicine rejected, currently considered for Respiratory Research
- **Comorbidity in IPF patients from EMPIRE registry (European Multipartner IPF registry)**
 - 1 st author professor Jovanovic, sent for comments to the SC members, additional small analysis done



Analysis in process

- **Analysis: Cytological profile of bronchoalveolar liquids in Czech patients from EMPIRE IPF Registry**
 - Dr. Lošťáková – will be presented by in November
- **3 analysis aimed on genetic polymorfisms in Czech patients from EMPIRE IPF Registry**
 - Dr. Lošťáková, Doc. Kriegrová, Dr. Doubková
 - analysis are focusing on drug metabolism, MUC5B polymorfism, TERT/ TERC genes mutations, we are waiting for parameters to be specified
- **Transplantation survey**
 - Prof. Kramer, we are waiting for analysis specification





EMPIRE
(IPF)

IIS Study proposals

Proposal of professor Jovanovic regarding blood sample biomarkers

- Team of prof. Jovanovic has performed in 23 IPF patients Soluble sPD-L1 test to determine concentrations in blood (in fact plasma). Obtained results, already in part presented at WASOG, will be presented as Thematic Poster on Tuesday at the ERS Congress. They have done also membrane PD-L1 expression, regarding the available surgical biopsy IPF tissue samples (only 12). The article is in the press.
- Prof. Jovanovic has now enough leftover of the platform for this sPD-L1 blood test, (nearly for app. 400 analysis) and is be able to provide it to EMPIRE team to have Joint Project on this issue, which would be performed free by her colleague, biochemist, Prof Jelena Kotur.
- The only cost would be the transport of biological material - blood

*WASOG = International Conference on Sarcoidosis and Interstitial Lung Diseases



Risk stratification model for IPF patients - proposal of professor Mogulkoc

- EMPIRE is the world's largest IPF database.
- It allows a survival analysis of unprecedented power.
- From this data, it should be possible to **extract prognostically significant factors and to combine them in a calculator model that clinicians can use to predict survival.**
- The calculator should be usable at presentation and at subsequent reassessments. There is a precedent for such calculators from pulmonary arterial hypertension.
- Prognostic indicators in IPF have been identified. [PFT FVC (>70%; 56 months, 55 to 69; 41 months <55%; 29 months) DLCO, 6MWT distance (<250, 250 to 380, >380) and saturation, Oxygen requirement, Comorbidities, Dyspnoea score, Cough score, HRCT score, GAP gender, age, FVC, DLCO, CPI (FVC DLCO FEV1), BMI, Hospitalisation, for respiratory reasons, FVC loss in 6 to 12 months >10%, 6MWT loss of more than 50 m in 6 months, Acute exacerbation, Lead time bias.
- Must be usable even with missing data.
- At reassessment, the patients with the most severe disease will have died. There will be new longitudinal factors based on changes in parameters.
- Simple calculators can be paper-based. More complex calculations need to be web- or app-based.



Relationship between IPF and cancer - proposal of professor Mogulkoc

- Professor has already recorded 512 cases to the EMPIRE registry, among whom 51 had cancer at various sites.
- There were 30 with lung cancer.
- In order to do the analysis, she needs more information than EMPIRE gives, for example, the diagnostic modality, the pathological type, size and stage, location of the tumour (peripheral or central for lung cancer), and the treatment of the tumour.
- Discussion: Is it feasible to collect this additional cancer information for those patients who develop a malignant neoplasm ?



IIS study proposals

- **Planned IIS studies**
 - Any new suggestions?





EMPIRE
(IPF)

eCRF changes

Changes in eCRF

- In Follow-up form information about O₂ saturation has been specified:
O₂ saturation by pulse oxymeter
- Added possibility to fill **blood gases (O₂, CO₂) in mmHg or kPa units**



GAP Score

- If diffusion capacity (TL_{co}) values has **not been filled**, question **why are they missing** has been added
 - Option „*Unable to fill them*“ means, that the GAP score value will increase + 3 points
 - All patients that did not have it filled will automatically have assigned answer – „*Unknown reason before the database update*“

FEV1 (% EV)

- FEV1 (% EV) is now counted with a **new formula**
- $FEV1 \text{ MEN} = (FEV1 (l) * 100) / (4,3 * \text{HEIGHT (M)} - 0,029 * \text{AGE (YEARS)} - 2,49)$
- $FEV1 \text{ WOMEN} = (FEV1 (l) * 100) / (3,95 * \text{HEIGHT (M)} - 0,025 * \text{AGE (YEARS)} - 2,6)$
- Tiffeneau-Pinelli index (FEV1/FVC) is left as a separate item

Source: Quanjer, G.J. Tammeling, J.E. Cotes, O.F. Pedersen, R. Peslin, J-C. Yernault. Lung volumes and forced ventilatory flows, Ph.H, *European Respiratory Journal* 1993; 6: 5-40; DOI: 10.1183/09041950.005s1693



CPI index

- CPI index formula has been added to the follow-up form
 - $\text{CPI index} = 91 - (0,65 \times \% \text{DLCO}) - (0,53 \times \% \text{FVC}) + (0,34 \times \% \text{FEV1})$
-

To be added:

- Duration of symptoms at the time of diagnosis establishment (months) will be given maximum upper borderline 1000 (months) with a warning message sent at 480 (months)





EMPIRE
(IPF)

Rules of the registry, Contracts, Payments

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** (or unless otherwise agreed with BI in individual cases) – you can send it to me and I will resend it to BI
- To check if 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 BI support



Contracts with the centres

- **From second Quarter - April 2018 only contracts with the centres (hospitals) are possible**
- According to the new regulations that the Masaryk University had implemented and anticorruption law of the Czech Republic it is no longer possible to make agreements with datamanagers (investigators) directly
- Contract templates have been sent to all centres, the centres are obliged to pay the remuneration to the datamanagers
- Please try to go through them and sign them as soon as possible, also try to remind it to the centres from your country. If the contracts are not signed we are not able to send the payments



Anonymisation of the patients

- **Initials and date of birth of the patients** will be **deleted** from the database in order to anonymise the patients in beginning of 2019, instead just information about **month and year of birth** will stay in the database
- ID stays the same IPF-XY13-212
- Physicians should take care of the way, how they should identify the patient
- There will be email sent by HelpDesk informing about this situation (possibly with a xls. table consisted of IDs, initials, date of birth and informed consent (IC) question for each centre)
- For the patients in which the **IC is missing, it should be provided**, each of the patients should **sign new version of IC**



Third parties involvement

- There has to be an **confidentiality/cooperation agreement** signed between the University and any third party that would like to get any information from the EMPIRE Registry
- The agreement can only be signed after the SC approval about the cooperation with the third party
- In the agreement there should be specified the purposes and motivation to get any information from EMPIRE, the outcomes the person is planning to make, the specific parameters he/she would like to receive, declaration that the person has no further intention with usage of the data, is aware of his/hers responsibilities, agrees to the conditions of EMPIRE and IBA FM MU and will provide the outcomes to the Steering Committee and IBA for comments before the actual publication





EMPIRE
(IPF)

TIME for discussion

Damir Herman proposal

- Physicist with extensive experience in cancer and auto-immune disease research Damir Herman from the Silicon Valley (US) contacted us with proposal on working on the tertiary outcomes of EMPIRE (to describe real life approach to IPF in participating countries in CEE – diagnostic algorithm, treatment patterns/outcomes, resource utilization; to determine No of patient suitable for enrolment in clinical trials)
- He had these suggestions:

„I would like to apply several machine learning algorithms and optimize analyses to assign probabilities of having IPF for new incoming patients very early on. I would also like to understand how to provide data-driven decisions about therapy.

Since you have already addressed the primary (IPF incidence and prevalence) and secondary outcomes (description of basic characteristics of patients with IPF), now is the right time to focus on the tertiary outcomes which addresses the question my cousin's friend's dad (IPF patient) had: "Doc, how is this relevant for me?" So this is where I can come in and grab the bull by the horns. “



ARIANE IPF

- Meta-registry – allows metaanalyses of existing registries
- At the beginning 6-10 IPF Registries together
- Afterwards defining of the variables/ data fields
- Then funding question (so far CRC-ERS 30 000€/ 3 years)



External presentation of the EMPIRE Registry

- EMPIRE Registry should be presented as a whole, one international registry, not one national registry



Any other business





EMPIRE
(IPF)

**Thank you for your time and
attendance on the 8th international
SC meeting!**